ABSTRACTS OF WORLD MEDICINE

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Pathology

1. Comparison of the Granuloma Producing Capacity of Normals and Sarcoid Granuloma Patients: Experimental Analysis of the Sarcoid Diathesis Theory

H. J. HURLEY and W. B. SHELLEY. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **237**, 685–692, June, 1959. 2 figs., 13 refs.

In an investigation carried out in the Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, an attempt was made to assess the significance of the widely held view that a sarcoid diathesis determines the development of sarcoid granulomata in susceptible individuals. Intradermal injections of homologous whole blood and solutions of sodium stearate, beryllium, silicon, zirconium, and 70 other elements of the periodic table were administered to 300 healthy male volunteers, to 35 patients with sarcoidosis, and to 6 patients with zirconium deodorant granulomata.

The skin test sites were observed daily for 2 weeks and then at weekly intervals for 3 months. Biopsy specimens were obtained from persistent papules, 100 such specimens being examined. Sodium stearate provoked non-specific granulomatous reactions in some members of all three groups, but not characteristic sarcoid granulomata. Zirconium provoked sarcoid granulomata within one month, but only in patients with zirconium deodorant granulomata. The authors were therefore unable to demonstrate a sarcoid diathesis in which non-specific intradermal stimuli led to the development of sarcoid granulomata. They conclude that a specific granulomagenic substance is responsible for the production of this peculiar tissue response.

[This elaborate investigation provides strong evidence for the specificity of the Kveim test in sarcoidosis, the beryllium patch test in berylliosis, and the zirconium skin test in cases of deodorant granulomata.]

D. Geraint James

2. The Protein Distribution of Gastric Juice Electrophoresis; a Distinctive Pattern in Pernicious Anemia and Achlorhydria

I. KATZKA. *Gastroenterology* [*Gastroenterology*] **36**, 593–598, May, 1959. 5 figs., 11 refs.

The distribution pattern of proteins in human gastric juice has been studied by means of starch zone electrophoresis at Long Island Jewish Hospital, New Hyde Park, New York. Samples of natural gastric juice (6 to 10 ml. containing 0·1 to 0·3% of protein) from 10 healthy subjects, 7 patients with duodenal ulcer, 2 with gastric ulcer, one with marginal ulcer, 4 with pernicious anaemia, and 2 with achlorhydria after histamine were examined in an electrophoretic apparatus; the gastric juice from 6 subjects who had received a subcutaneous injection of 1 mg. of histamine phosphate was also examined.

The electrophoretograms for the normal subjects showed 4 major peaks, designated A, B, C, and D, and in some cases 5 sub-peaks, A_1, A_2, and C_1, C_2, and C_3. The patients with peptic ulcer exhibited similar peaks, except that peak C tended to be higher than in the normal subjects; this enhancement appeared to correlate with the activity of gastric secretion rather than with the disease itself. In the gastric juice of the patients with pernicious anaemia or histamine achlorhydria, however, peaks A and C were absent in all but one and peak D was absent in all, whereas peak B was greatly accentuated; it is suggested that this protein distribution pattern probably indicates atrophy of the gastric mucosa. The electrophoretogram of saliva from the normal subjects also showed a large B peak. *J. E. Page*

3. Studies on Protein-bound Carbohydrates in Human Serum and Urine in Proteinuria. [Monograph]

B. LAURENT. *Scandinavian Journal of Clinical and Laboratory Investigation* [*Scand. J. clin. Lab. Invest.*] **10**, Suppl. 32, 1–84, 1958. 16 figs., bibliography.

4. Serum Haptoglobins in Hepatobiliary Disease

J. A. OWEN, I. R. MACKAY, and C. GOT. *British Medical Journal* [*Brit. med. J.*] **1**, 1454–1457, June 6, 1959. 3 figs., 18 refs.

At the Walter and Eliza Hall Institute of Medical Research, Melbourne, the authors have assessed the clinical and diagnostic value of measurement of the serum haptoglobin level as an index of hepatic function. The serum haptoglobin level was estimated in terms of the amount of haemoglobin (Hb) which must be added to the serum to saturate the haptoglobins present.

In 50 healthy blood donors the average value was 84 (range 30 to 200) mg. Hb per 100 ml. In 5 cases of acute infective hepatitis and 26 of chronic hepatitis low values were obtained except in a few cases in which liver function was good. Only in 3 of 13 patients with nutritional cirrhosis (due to alcoholism) were low values obtained, the remainder being normal. The values in 12 cases of extrahepatic biliary obstruction were either normal or increased, being over 200 mg. Hb per 100 ml. in 4 cases.

Jaundice was present in 32 patients. The serum haptoglobin level was high in 12 of these with extrahepatic biliary obstruction, low in 14 with acute or active chronic hepatitis, and normal in the remainder, who had nutritional cirrhosis. Low serum haptoglobin levels were, on the whole, associated with low serum albumin levels and high serum glutamic oxalacetic transaminase levels.

It is concluded that the measurement of serum haptoglobin levels is of value in assessing the degree of hepatocellular damage and in the differential diagnosis of jaundice. *M. Lubran*

5. **Bromsulphalein Movement in Decompensated Portal Cirrhosis**

L. S. Monroe and A. Kittinger. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **53**, 901–905, June, 1959. 3 figs., 9 refs.

The "bromsulphalein" clearance test has for many years been accepted as the most sensitive indication of hepatic damage in non-jaundiced patients. In performing the test the dose of the dye is usually calculated on the basis of body weight (5 mg. per kg.) on the theory that this reflects the circulating fluid volume. However, in patients with severe ascites up to 30% of the body weight may be represented by the ascitic fluid, and it seemed to the authors that a change in weight, due for example to a recent paracentesis, could alter the test result without there being any real change in hepatic function. In this paper from the Schripps Clinic and Research Foundation, La Jolla, California, they describe an investigation into the movement of bromsulphalein between the blood and ascitic fluid in 4 patients with decompensated portal cirrhosis and ascites.

To ascertain if bromsulphalein passed from the blood into ascitic fluid 600 mg. of the dye was introduced intravenously in 2 patients by slow drip over a period of 2½ hours. The blood dye level was kept between 3 and 6 mg. per 100 ml. during this time and samples of ascitic fluid and blood were withdrawn at intervals for 5 hours. After this time the blood still contained significant levels of the dye, but despite this no bromsulphalein was found in the peritoneal fluid at any time during the sampling period. The movement of bromsulphalein out of the ascitic fluid was then observed in 3 cases after the intraperitoneal injection of 150 mg. of the dye. As before blood specimens were taken at frequent intervals, while sampling of the peritoneal fluid was continued for 5 to 7 days. The fall in peritoneal bromsulphalein concentration was slow, significant amounts (0·3 and 0·7 mg. per 100 ml.) being detected in 2 of the patients after 4 and 6 days respectively. At no time could bromsulphalein be detected in the blood.

These results suggest that the transfer of bromsulphalein from the blood to the ascitic compartment and vice versa is at such a slow rate that the weight of the ascitic fluid should be considered in the calculation of the dose of the dye, since failure to allow for this would result in the administration of an excess amount of dye, with subsequent elevation of its level in the blood. It has been shown that when injected intravenously or intraperitoneally bromsulphalein becomes bound to the serum albumin fraction and that the turnover of albumin between the peritoneal and vascular compartments is slow (0·4 to 0·65 g. per hour). Thus a bromsulphalein dilution technique can be used to determine the amount of ascites present. *G. Clayton*

MORBID ANATOMY AND CYTOLOGY

6. **Bronchiolar (Peripheral Lung) Neoplasms and Previously Undescribed Observations on the Origin of Bronchiolar Carcinoma**

S. L. Eversole and W. F. Rienhoff III. *Journal of Thoracic Surgery* [*J. thorac. Surg.*] **37**, 750–765, June, 1959. 18 figs., 9 refs.

An occasional finding in routine necropsy material is a subpleural nodule which, on histological examination, is seen to be a small bronchiolar adenomatous tumour or malformation. In this paper from the Johns Hopkins University School of Medicine and Hospital, Baltimore, 4 cases are described in which this lesion was an incidental necropsy finding. The smaller lesions, seen in 2 of the cases, were probably malformations, while the larger lesions in the remaining 2 cases had characteristics of frank tumour at the periphery. In 2 cases of localized bronchiolar carcinoma surgically treated there was a striking similarity of appearance; it is therefore suggested that bronchiolar carcinoma may arise from bronchiolar adenomatous malformations.

One further case is described in which a subpleural nodule was found incidentally at necropsy, this lesion being an example of a single small focus of pulmonary adenomatosis. The histological picture in this case differed from that in the cases of bronchiolar carcinoma. It is pointed out that in the literature pulmonary adenomatosis and alveolar-cell carcinoma "are indiscriminately grouped with bronchiolar carcinoma"; in the authors' view the last-named is different in nature and should not be grouped with the others.

A. W. H. Foxell

7. **A Comparison of the Histopathology of Tracheal and Bronchial Epithelium of Smokers and Nonsmokers**

G. Ide, V. Suntzeff, and E. V. Cowdry. *Cancer* [*Cancer (Philad.)*] **12**, 473–484, May–June, 1959. 5 figs., 22 refs.

A comparative investigation of the changes in the epithelium of the bronchus and trachea in smokers and non-smokers was carried out at the Wernse Cancer Research Laboratory, Washington University School of Medicine, St. Louis, Missouri, necropsy material from the following six groups of patients being studied: (1) non-smokers, 23; (2) non-smokers with pneumonia, 4; (3) light smokers, 31; (4) light smokers with pneumonia, 19; (5) heavy smokers, 12; and (6) heavy smokers with pneumonia, 4. Transverse and longitudinal sections in addition to whole mounts were examined in respect of: (*a*) the thickness of the epithelium; (*b*) the length of the cilia; (*c*) the percentage of goblet cells; (*d*) the incidence of a basal-cell hyperplasia

and squamous-cell metaplasia; and (*e*) the presence of atypical cells and mitotic figures. [It is not possible to summarize the findings and the paper must be read in full.] In general, the tracheal and bronchial epithelia reacted in an essentially similar way, except that squamous metaplasia was found more frequently in the trachea than in the bronchus of light smokers. In all except the non-smokers the epithelium was thickened and the cilia were shorter and reduced in number. The percentage of goblet cells was increased in light smokers and reduced in heavy smokers [but the authors do not state whether any bronchitis was present which might have been related to their findings]. They discuss at some length the reasons for their finding that "the incidence of tracheal cancer has not increased with the increase in cigarette smoking to anything like the increase in the incidence of bronchogenic carcinoma".

G. J. Cunningham

8. **Bronchiolar Proliferation and Metaplasia Associated with Bronchiectasis, Pulmonary Infarcts, and Anthracosis**

S. W. BERKHEISER. *Cancer* [*Cancer (Philad.)*] **12**, 499–508, May–June, 1959. 14 figs., 15 refs.

A study of the incidence of various histological types of bronchiolar proliferation in surgical and necropsy specimens of lung tissue from a series of 46 known cases of bronchiectasis, 47 of anthracosis, and 52 of pulmonary infarction is reported from Harrisburg Polyclinic Hospital, Pennsylvania. The proliferative reactions found were of approximately the same general types, and atypical squamous- and basal-cell metaplasia was observed in all three diseases, although its incidence was higher in the cases of anthracosis (6·4%) than in those of bronchiectasis (4·3%) or of pulmonary infarction (3·8%). On the other hand adenomatous proliferation of the bronchiolar epithelium was found in 24% of the cases of bronchiectasis, 15·4% of those of pulmonary infarction, and 10·6% of those of anthracosis. As found by other workers, these foci of proliferation occurred in areas where lung tissue had been destroyed and often in fibrotic foci.

The relationship between these reactions and early bronchogenic carcinoma is discussed and it is pointed out that since the atypical metaplastic cells found in association with chronic pulmonary disease may be cytologically indistinguishable from malignant cells there is a possibility that in such cases a false positive result may be obtained on examination of sputum for cancer cells. [In a small series of cases of bronchiectasis examined by Cunningham *et al.* (*Thorax*, 1958, **13**, 64; *Abstr. Wld Med.*, 1958, **24**, 243) no evidence of a cancerous process was found.] Reference is made to the work of Auerbach *et al.* (*Cancer (N.Y.)*, 1956, **9**, 76; *Abstr. Wld Med.*, 1956, **20**, 91), who found a direct relationship between smoking habits and the incidence of foci of basal-cell hyperplasia and squamous-cell metaplasia in the bronchi. [The present author has not emphasized that these lesions were found predominantly in larger bronchi and that it is not at all certain that they are directly related to the changes in the smaller terminal bronchioles which he described.] *G. J. Cunningham*

9. **The Cause of Death in Haemolytic Disease of the Newborn.** (Zur Todesursache beim Morbus haemolyticus neonatorum)

K. DIEMER and H. BECHTELSHEIMER. *Zeitschrift für Kinderheilkunde* [*Z. Kinderheilk.*] **82**, 147–152, 1959. 1 fig., 29 refs.

The authors analyse 14 cases of haemolytic disease of the newborn in which post-mortem examination was carried out at the Pathological Institute of the University of Mainz during the 4 years 1955–8. The patients could be divided into two main groups. The first consisted of 3 babies aged 4 to 7 days who died with the clinical picture of kernicterus, having been admitted to hospital too late for exchange transfusion to be carried out. In all 3 the diagnosis was confirmed at necropsy. The second group consisted of 11 babies, of whom one was stillborn and all the others had died within the first few hours after birth, none being more than 24 hours old.

In all cases the diagnosis of haemolytic disease of the newborn was confirmed clinically or serologically, or both. Each of the liveborn babies died suddenly with signs of cardiac insufficiency, no clinical evidence of kernicterus being found in this group. Post-mortem examination of the heart revealed severe, diffuse myocardial damage, the changes resembling those of hydropic degeneration. Many of the muscle fibrils contained vacuoles filled with fluid, with distortion of the nuclei, while others were considerably swollen and there was widespread fibrillolysis. *E. Forrai*

10. **Morphological Findings in the Lymph Nodes in Infectious Mononucleosis.** (Morphologische Befunde an Lymphknoten bei infektiöser Mononukleose)

H. REINAUER. *Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medizin* [*Virchows Arch. path. Anat.*] **332**, 56–82, 1959. 16 figs., bibliography.

In this [very long] paper from the Pathological Institute of the Düsseldorf Medical Academy the findings as determined by both light and electron microscopy in lymph nodes removed from 3 cases of infectious mononucleosis are described in detail. One node was removed in the acute stage of the disease, the others in less acute stages; all nodes were taken from the groin.

In the acute phase light microscopy showed that there was oedema of the tissue, proliferation and enlargement of reticulum cells, and obliteration of the sinusoidal spaces. The cortex contained small follicles with reactive centres. In the medullary region reticulum cells and other types of cell were seen to encroach on the sinusoids. The sinuses contained vacuolated cells, degenerate cells and their fragments, large mononuclear leucocytes, lymphocytes, and some plasma cells. The reticuloendothelial cells contained Schiff-positive staining material. In the later stages of the disease there was an increase in the number of plasma cells and macrophages, while the sinusoids were wide and patent and contained many mononuclear cells.

Examination by the electron microscope revealed debris in the sinusoids. The vacuolated cells were

studied extensively and a detailed report is given of normal appearances. An interesting feature was the finding of particles resembling viruses in macrophages and other cells. These particles ranged in diameter from 108 to 176 mμ and had a distinct outer membrane.

[The paper contains a wealth of detail and good illustrations, but suffers from a lack of integration.]

G. Loewi

11. **Histology of the Aorta in Coarctation**

M. S. DUNNILL. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **78**, 203–207, 1959. 4 figs., 14 refs.

The histological appearances of the aorta in coarctation were studied at the Radcliffe Infirmary, Oxford, in 9 cases in which the degree of coarctation was such that the stenosed segment would not admit a wire probe. Atheromatous changes were present in the intima proximal to the coarctation in 6 cases and distal to the coarctation in 2 only, in both of which the diastolic pressure in the legs was abnormally high. The media showed focal increase in sulphated mucopolysaccharide (metachromatic in azure-A preparations), often with destruction of elastic fibres. These changes were most marked when the diastolic pressure was raised. The Gsell type of degeneration with cyst-like changes in the media, seen in 2 cases, was considered to be artefact, due to delay in fixation followed by dehydration in alcohol, developing in aortas with an increase in mucopolysaccharide.

The media distal to the coarctation was as thick as that proximal to it, but the elastica differed in the two segments. In all except one case the number of elastic laminae in the tunica media proximal to the coarctation was greater than the number distal to it. This was most noticeable in the older patients and in those in whom there was a big difference between the blood pressure in the arms and that in the legs. In the one case in which the number of laminae distal to the coarctation was in excess of the number proximal to it the diastolic pressure in the arms and legs differed by 5 mm. Hg only, and the blood pressure in both was within normal limits.

These findings lend support to the views that " hypertension is an important factor in the production of atheroma " and that " the stimulus of variation in pressure may be necessary for the formation of elastic tissue ".

H. Caplan

12. **Demonstration of a Characteristic Malformation of the Neuromuscular Junction in Myasthenia Gravis.** (Mise en évidence d'une malformation caractéristique de la jonction neuromusculaire dans la myasthénie)

C. COËRS and J. E. DESMEDT. *Acta neurologica et psychiatrica Belgica* [*Acta neurol. belg.*] **59**, 539–561, May [received July], 1959. 13 figs., 15 refs.

In this study reported from the Departments of Neurology and Morbid Anatomy of the University of Brussels the authors have clearly shown for the first time that a characteristic morphological abnormality may exist in myasthenia gravis. In 6 well proven cases of the disorder examined electromyographically biopsy specimens of the affected muscles were studied by the intravital methylene blue staining method and the acetothiocholine method for showing the subneural apparatus, as well as by the usual standard qualitative and quantitative histological techniques.

The authors describe two types of abnormal terminal innervation. (1) The dysplastic ending, which is characteristic of myasthenia and which, because it had been previously seen in a congenital case of the disease, they believe to be the primary malformation. In this type, in place of the normal " spray " ending at the motor end-plates, the fibres form an elongated nodular ribbon along which the subneural apparatus is situated. This change was found in from 5 to 45% of motor end-plates examined in 4 of the 6 cases; it was not associated with any other structural abnormality in the muscle fibres. (2) The second change, which was present in 3 of the 6 cases, is one not specific for myasthenia. The authors have termed it the dystrophic ending, for it has been demonstrated both in primary dystrophies and in myositis. In one of these 3 cases there were also degenerative changes in the muscle fibres. They suggest that it is possible, on the basis of these observations, to divide cases of myasthenia gravis into two nosological groups: one, perhaps constitutional, showing dysplastic nerve endings and the other, which is less well defined, having some atypical features, but electrically and functionally identical with the first, while not showing this specific feature. Further studies of more cases will be needed before this important concept can be finally confirmed.

J. B. Cavanagh

13. **Mixed Tumors of the Skin of the Salivary Gland Type**

A. P. STOUT and J. G. GORMAN. *Cancer* [*Cancer (Philad.)*] **12**, 537–543, May–June, 1959. 7 figs., 28 refs.

To determine whether malignant changes occur in mixed tumours of the skin of sweat-gland origin the authors studied the findings in 39 cases recorded in the files at Columbia University College of Physicians and Surgeons, New York, and 95 cases which have been reported in the literature.

Two-thirds of the tumours occurred on the head and face, and the majority of the patients so affected were males; there was no sex difference in the incidence of tumours on other parts of the body. The authors state that " unquestionably malignant tumours develop from sweat glands " [type not specified] but in the present series of cases there was no evidence of malignancy in a mixed tumour of sweat-gland origin. In the series of 39 cases there was only one, that of a girl of 15 months, in which the tumour was considered to be both mixed and malignant. Unfortunately, no follow-up record after operation was available, but the authors state that the location of the tumour in the cheek made it " more probable that it came from the parotid salivary gland instead of from sweat glands ". They also describe an unusual case, in a woman of 31 years, of a tumour below the medial condyle of the knee; the histological appearances were those of a mixed salivary tumour, but the growth lay entirely beneath the deep fascia.

Bernard Lennox

Microbiology and Parasitology

14. **Some Results of the Study of Adenoviruses.** (Некоторые итоги изучения аденовирусов)
R. S. Drejzin and V. N. Ždanov. *Журнал Микробиологии, Эпидемиологии и Иммунобиологии* [*Ž. Mikrobiol. (Mosk.)*] **30**, 3–11, May, 1959.

This report of the first investigation of the adenoviruses in the Soviet Union shows that the facts established by similar studies carried out in the U.S.A. and in Great Britain since 1953 largely hold good for Eastern Europe as well.

In 52 out of 615 patients with acute respiratory infections strains of adenovirus were present in the nose, sputum, conjunctiva, or faeces, and could be isolated as late even as the 14th day after the start of the illness. In 5% of 417 further patients with similar symptoms a rise in the titre of complement-fixing antibody to adenovirus was established. Type-3 virus was isolated in 50% of the positive cases, the other strains frequently found being Types 1, 4, 5, and 6.

It was shown that 14 cases of membranous conjunctivitis, clinically diagnosed as diphtheria affecting the eye, were due to adenovirus infection, 12 of them being due to Type-3 virus; the remaining 2 strains could not be typed. It is claimed that the finding of adenovirus in membranous conjunctivitis has not been previously described. As in the U.S.A. Types 1, 2, and 5 could be isolated from adenoids and tonsils removed at operation. The authors consider that the cytological changes, particularly the peeling off of small pieces of cell material from the wall of roller-tube cultures of infected HeLa cells, are highly characteristic for adenovirus and enable a diagnosis by inspection or histological sections to be made.

K. Zinnemann

SEROLOGY AND IMMUNOLOGY

15. **The Determination of Coagulase in *H. pertussis*.** (К вопросу об определении коагулазы у H. pertussis)
G. I. Mar and S. I. Solovbjančik. *Журнал Микробиологии, Эпидемиологии и Иммунобиологии* [*Ž. Mikrobiol. (Mosk.)*] **30**, 55–58, May, 1959.

In 1955 Billaudelle (*Acta path. microbiol. scand.*, 1955, **5**, 37) showed that 6 strains of *Haemophilus pertussis* in Phase I possessed a powerful coagulase which led to the formation of a clot in rabbit and sheep plasma within 15 to 30 minutes. In the present paper this observation has now been confirmed with 34 different pertussis strains from various sources in the U.S.S.R., both in Phase I and Phase II. The majority of strains formed a clot within 15 to 30 minutes, but 4 strains did so only after 1 hour and 6 only after 2 hours. Clotting occurs both at room temperature and at 37° C. One strain of *H. parapertussis* formed a clot after 2 hours. Plasma from various species of animal was investigated, but clot formation was observed only with sheep plasma. The quantities used were 0·5 ml. of plasma and 0·3 to 0·03 ml. of a suspension (in 5 ml. of saline) obtained from 3 plate cultures after 48 hours of growth. Observations were not continued beyond 7 hours, and thus the dissolving of the clot, seen regularly by Billaudelle after more than 7 hours' incubation, was not noted. The authors suggest that the presence of coagulase in a strain of *H. pertussis* may be related to its pathogenicity.

[Billaudelle had suggested only that the high viscosity of pertussis sputum might be due to the coagulase of the causative organism.] *K. Zinnemann*

16. **Rapid Identification of *Pasteurella pestis* with Fluorescent Antibody. I. Production of Specific Antiserum with Whole Cell *Pasteurella pestis* Antigen**
C. C. Winter and M. D. Moody. *Journal of Infectious Diseases* [*J. infect. Dis.*] **104**, 274–280, May–June, 1959. 20 refs.

In the series of studies here reported from the U.S. Public Health Service Communicable Disease Center, Atlanta, Georgia, antisera of high titre and specificity for *Pasteurella pestis* were produced in rabbits by the intravenous injection of various antigenic preparations, consisting of whole cells, crude Fraction 1 (the supernatant from whole-cell preparations), Fraction 1 (the ammonium sulphate precipitate from crude Fraction 1), and somatic substance (Koschka-type) of *Past. pestis*. Polyvalent and group specific antigens were also prepared from *Past. pseudotuberculosis*. Full details of the method of preparation of these antigens are included in the paper.

The antisera thus produced were tested against a number of strains of *Past. pestis* and *Past. pseudotuberculosis*. The antisera produced by the whole-cell and the Fraction-1 antigens gave high titres and were quite specific, all of 29 strains of *Past. pestis* being agglutinated whereas none of 19 strains of *Past. pseudotuberculosis* were. Crude Fraction-1 antisera agglutinated both *Past. pestis* and *Past. pseudotuberculosis*, whereas the somatic-substance antigen (Koschka) agglutinated all 19 strains of *Past. pseudotuberculosis* but none of the strains of *Past. pestis*. The antisera produced against various strains of *Past. pseudotuberculosis* also proved to be highly group specific, the polyvalent serum agglutinating all 19 strains of *Past. pseudotuberculosis* but none of the 29 strains of *Past. pestis*.

From the results of this investigation the authors conclude that a highly specific antiserum could be produced, providing that the organisms are grown under conditions conducive to the production of large amounts of Fraction 1 and that the immunization schedule is short; these conditions involve culturing a fully virulent strain of *Past. pestis* in casein hydrolysate glucose mineral

broth for 72 hours at 37° C., killing the culture with 0·4% formalin, and immunizing rabbits with this antigen given in 3 injections over a period of one week.

R. F. Jennison

17. **Rapid Identification of *Pasteurella pestis* with Fluorescent Antibody. II. Specific Identification of *Pasteurella pestis* in Dried Smears**

C. C. WINTER and M. D. MOODY. *Journal of Infectious Diseases* [*J. infect. Dis.*] **104**, 281–287, May–June, 1959. 3 figs., 8 refs.

This second paper deals with the use of the antiserum described above [see Abstract 16] to prepare a fluorescein-labelled antiglobulin solution for the detection and identification of *Pasteurella pestis* in simple dried smears from pure cultures. The globulin was precipitated by ammonium sulphate from the antiserum prepared against whole cells of *Past. pestis* and conjugated with fluorescein *iso*cyanate. Similar preparations of globulin were also made from the serum of non-immunized rabbits and rabbits immunized with the somatic antigen, as previously described. Details of the staining technique are given.

It was found that smears fixed with methanol or ethanol were unsatisfactory, but fixation with heat or dioxane gave very good results with formalin-killed cultures. Dried smears prepared from live organisms and fixed with 0·5% formalin also gave very good results, although the number of organisms in the smears was diminished. It was possible to demonstrate the specificity of the fluorescent staining by absorption and inhibition tests. Staining could also be produced with the globulin from the antiserum prepared against the somatic-substance antigen, providing the organism had been subjected to conditions which exposed the " envelope " antigen, for example, by heating at 60° C. for 30 minutes. Further experiments to determine the stability of the fluorescent antibody showed that solutions were stable for at least one year after storage under various conditions, but that storage at 0·5° C. resulted in a more satisfactory reagent than frozen or lyophilized preparations.

In tests of the specificity of the reagent carried out on 100 strains of bacteria it was demonstrated that, apart from one virulent strain and 2 avirulent strains, all 33 strains of *Past. pestis* were brilliantly stained, provided that the organisms were produced under conditions which enhanced the production of Fraction 1. It was further shown that the virulent strain not stained did not produce any Fraction 1. No strain of *Past. pseudotuberculosis* or other bacterial strains were stained.

R. F. Jennison

18. **Rapid Identification of *Pasteurella pestis* with Fluorescent Antibody. III. Staining *Pasteurella pestis* in Tissue Impression Smears**

M. D. MOODY and C. C. WINTER. *Journal of Infectious Diseases* [*J. infect. Dis.*] **104**, 288–294, May–June, 1959. 1 fig., 17 refs.

In this third study the authors investigated the possibility of making earlier diagnosis of plague infections by means of the specific fluorescent antibody described above [see Abstracts 16 and 17]. When mice were injected intraperitoneally with varying dilutions of *Pasteurella pestis* it was found that even if as few as 20 virulent plague bacilli were injected the organisms could be readily detected within 2 days in tissue smears stained with fluorescent antibody, being easily seen in the spleen, liver, lung, and heart blood. The presence of the *Past. pestis* was confirmed by conventional bacteriological methods, but this required at least 2 further days. When viewed under ultraviolet light the fluorescent bacilli could be readily distinguished from tissue materials. It was possible also to demonstrate specificity by absorption and inhibition tests.

Further experiments on infected mice treated with cortisone showed that administration of this steroid did not shorten the time required for diagnosis, but confirmed that the fluorescent-antibody staining technique gave a positive result 2 or 3 days earlier than the conventional methods, and further that when large inocula were employed the plague bacilli could be identified in the tissues after 24 hours.

The authors suggest that the method described could be used with benefit for the rapid identification of unknown specimens.

R. F. Jennison

19. **British Standard Poliomyelitis Antisera Types 1, 2, and 3**

F. T. PERKINS and D. G. EVANS. *British Medical Journal* [*Brit. med. J.*] **1**, 1549–1553, June 20, 1959. 5 refs.

Antisera to the three types of poliomyelitis virus were prepared in rhesus monkeys and freeze-dried. These preparations were then subjected to a collaborative study in five different laboratories under the auspices of the Medical Research Council in order " to determine whether different workers were able to obtain similar potency values when sera were assayed in terms of the freeze-dried preparations ". [For details of the procedure adopted and the techniques used the original paper should be consulted.]

The authors report as follows. " Close agreement was obtained between the different laboratories when the type 1, 2, or 3 neutralizing potencies of poliomyelitis antisera were determined with reference to freeze-dried preparations of antisera. It was therefore decided, with the agreement of those who participated in the study, to establish the three freeze-dried preparations of antisera as British Standard Poliomyelitis Antisera types 1, 2, and 3, and to assign to each a value of 10 units per ampoule. It will now be possible to express the neutralizing potency of sera in terms of units and to abandon the unsatisfactory method of using titre-dilutions ".

The authors state that the standard antisera will be held by the Department of Biological Standards, National Institute for Medical Research, Mill Hill, London.

J. E. M. Whitehead

20. **Vaccination against Poliomyelitis with Attenuated Live Virus.** [Review Article]

D. R. E. MACLEOD. *Canadian Medical Association Journal* [*Canad. med. Ass. J.*] **80**, 998–1001, June 15, 1959. 41 refs.

Pharmacology and Therapeutics

21. **Studies on a Long-acting Vitamin B_{12} Preparation**
R. E. THOMPSON and R. A. HECHT. *American Journal of Clinical Nutrition* [*Amer. J. clin. Nutr.*] **7**, 311–317, May–June, 1959. 4 figs., 12 refs.

The therapeutic value of vitamin B_{12} (cyanocobalamin) given parenterally in pure form or with certain bases is limited by the very rapid absorption and considerable urinary excretion of the drug. The present authors report a study of the long-acting properties of a cyanocobalamin–zinc-tannate preparation (C.Z.T.) given intramuscularly to human beings and rats. After injection in human beings of the equivalent of 500 μg. of vitamin B_{12} there was a marked rise in the serum vitamin-B_{12} level, which was sustained for 28 days or longer, and the urinary excretion was less than 2% of the injected dose. It is suggested that there is probably a steady transfer of the vitamin to body stores, so that C.Z.T. can satisfactorily replace depletion. *R. B. Thompson*

22. **Nicoumalone: a New Anticoagulant**
A. J. BRAFIELD. *British Medical Journal* [*Brit. med. J.*] **1**, 1211–1213, May 9, 1959. 1 fig., 9 refs.

The main action of nicoumalone (" sinthrome "), like that of other derivatives of coumarin, is to depress Factor VII and, later, prothrombin activity. The drug is not cumulative, being rapidly excreted unaltered in the urine. At Whipps Cross Hospital, London, the stability of the prothrombin level after administration of nicoumalone was studied in 269 patients (155 with coronary thrombosis, 107 with venous thrombosis, and 7 with arterial occlusion). The dosage was controlled by the prothrombin activity, which was estimated by Quick's one-stage method at least 3 times a week. The results were expressed as " percentage prothrombin activity ", the figures being obtained by reference to a prothrombin dilution curve. For purposes of comparison the results obtained in 117 patients given " indema " and 242 given " dindevan " (both drugs being preparations of phenindione) were recorded.

Early results indicated that a dosage of 12 mg. of nicoumalone on the first day and 6 to 8 mg. on the second day was sufficient to depress the prothrombin to the desired level of 20% activity. The maintenance dose varied slightly from case to case, but was usually 2 to 3 mg. given in a single dose in the evening. In patients receiving a maintenance dose of 2 to 4 mg. withdrawal of the drug resulted in a return to normal in 36 to 48 hours.

The constancy of the prothrombin levels obtained during maintenance therapy was studied, and for this purpose the results of all prothrombin tests were divided into three groups according to the activity, namely, less than 10%; 15 to 35%; and more than 60%. A total of 1,284 tests was carried out. Of these, 69·8% gave readings within the range 15 to 35%, 6·6% gave readings of 60% or more, and only 1% a reading of less than 10%. In 984 tests on patients receiving indema the corresponding figures for the three groups were 49·3%, 18%, and 1·5%, and in 1,344 tests on patients given dindevan they were 60·1%, 8·3%, and 1·2%.

These results indicate that a high degree of stability in the reduction of prothrombin activity may be expected with nicoumalone. The initial and maintenance doses were lower than those recommended by a number of American workers (details of which are given in a table). Only 2 cases of severe spontaneous haemorrhage occurred in the author's series, in both of which the prothrombin activity was less than 10%. *G. Clayton*

23. **Evaluation of Anticoagulant Therapy with Anisindione (Miradon)**
W. F. CONNELL and G. A. MAYER. *Canadian Medical Association Journal* [*Canad. med. Ass. J.*] **80**, 785–790, May 15, 1959. 5 figs., 11 refs.

A new derivative of indanedione, anisindione, an oral anticoagulant of prothrombinopenic type, was used for both short-term and long-term therapy in a series of 169 patients seen at the Kingston General Hospital, Ontario, between October, 1957, and September, 1958, treatment being controlled by the whole-blood coagulation time. The drug was given in a dosage of 500 mg. on the first day, 300 mg. on the second and third days, and 200 mg. on the fourth day. The daily maintenance dose ranged from 25 to 175 mg. A satisfactory therapeutic prolongation of the standard clotting time was achieved within 3 days in patients receiving 100 mg. of heparin initially; without heparin the clotting time reached a satisfactory therapeutic level in 4 days. As with other anticoagulant drugs, vitamin K_1 was an effective antidote.

The authors state that " as in previous studies " they were unable to demonstrate a significant correlation between the whole-blood clotting time and the one-stage prothrombin time (Quick). *A. S. Douglas*

24. **Dihydrochlorothiazide in Control of Ascites**
D. N. S. KERR, A. E. READ, and S. SHERLOCK. *Lancet* [*Lancet*] **1**, 1221–1223, June 13, 1959. 1 fig., 7 refs.

A small pilot study was carried out at the Postgraduate Medical School of London of the comparative efficacy of chlorothiazide and dihydrochlorothiazide in the control of ascites in patients with liver disease, with particular reference to the action of the two drugs on potassium excretion. Under controlled conditions 5 patients with liver disease, ascites, and oedema received two courses of diuretic treatment, one consisting of 4 doses at 6-hourly intervals of 500 mg. of chlorothiazide and the other of 4 doses at 6-hourly intervals of 50 mg. of dihydrochlorothiazide. The second course was given at least 5 days after the first. Both drugs promoted diuresis, with

increased urinary excretion of sodium, potassium, and chloride. There was no significant difference between the effects of the two drugs, except for a slight rise in the serum bicarbonate level after dihydrochlorothiazide which was not seen after chlorothiazide. The authors emphasize that in patients with liver disease supplementary potassium and regular estimation of the serum electrolyte values are as necessary during dihydrochlorothiazide therapy as during treatment with chlorothiazide.

Bernard Isaacs

25. **Hydrochlorothiazide: a Comparison with Chlorothiazide**

P. R. FLEMING, J. F. ZILVA, R. I. S. BAYLISS, and J. PIRKIS. *Lancet* [*Lancet*] **1**, 1218–1221, June 13, 1959. 4 figs., 13 refs.

The diuretic action of hydrochlorothiazide was studied at Westminster Hospital, London, in 10 oedematous patients, 4 convalescent patients without evidence of oedema, and 6 healthy subjects. In the two groups without oedema 25 to 100 mg. of hydrochlorothiazide by mouth induced a diuresis in 1 to 2 hours, which reached a maximum after 3 to 5 hours and waned after 11 hours. The diuresis was accompanied by loss of Na, K, Cl, and HCO_3 ions. The changes were qualitatively similar to those occurring after administration of chlorothiazide, except that hydrochlorothiazide caused rather less HCO_3 excretion. The natriuretic effect of a dose of 25 mg. of hydrochlorothiazide was comparable to that of a dose of 0·5 g. of chlorothiazide. Qualitatively similar results were obtained in the oedematous patients, hydrochlorothiazide being an effective diuretic in a dose about one-tenth that of chlorothiazide. The authors recommend a daily dose of 50 to 150 mg. of hydrochlorothiazide, supplemented by potassium when treatment continues for more than a few days.

Bernard Isaacs

26. **Relationship between Diuretic and Antihypertensive Effects of Chlorothiazide and Mercurial Diuretics**

W. HOLLANDER, A. V. CHOBANIAN, and R. W. WILKINS. *Circulation* [*Circulation*] **19**, 827–838, June, 1959. 5 figs., 21 refs.

At Massachusetts General Hospital (Boston University School of Medicine), Boston, the authors have investigated the relationship between the hypotensive and diuretic effects of chlorothiazide and mercurial diuretics.

In 20 healthy subjects given chlorothiazide in a dose of 250 mg. three times daily for 30 days, sodium intake being normal, there was no fall in blood pressure although an early diuretic effect occurred. In contrast, in 7 out of 12 hypertensive patients given 1 g. of chlorothiazide intravenously there was a reduction in blood pressure which varied from 20/15 mm. to 60/30 mm. Hg, the hypotensive effect lasting for 24 to 48 hours and being accompanied by a significant diuresis. There was no change in the blood pressure in normal subjects given chlorothiazide parenterally, although a similar diuresis occurred, with proportional weight loss. The parenteral administration of mercurial diuretics (mercaptomerin or meralluride) also produced a significant hypotensive effect in 8 out of 15 hypertensive patients, the blood pressure falling by 15/10 mm. to 60/40 mm. Hg; this effect lasted for 24 to 54 hours. There was no fall in blood pressure in the normal subjects, although both the normal subjects and the patients had a significant and comparable diuresis.

Balance studies in 6 of the hypertensive patients showed that the reduction in blood pressure produced by chlorothiazide or the mercurials was accompanied by a cumulative negative sodium balance of between 150 and 200 mEq., but this also occurred in hypertensive splanchnicectomized patients during a net sodium loss of as little as 50 mEq. Further, the hypotensive effect of the diuretics persisted after the drugs had been withdrawn and the sodium intake restricted to 9 mEq. per 24 hours, even though in these patients sodium restriction alone (before administration of the diuretic drugs) had had no significant hypotensive effect. When the hypertensive patients were given 9α-fluorohydrocortisone together with chlorothiazide the sodium deficit was corrected —yet the blood pressure did not return to its original level, and some hypotensive effect persisted. When an aldosterone antagonist (SC 8109) was added to the chlorothiazide given to these patients a further fall in blood pressure occurred to a level below that produced by chlorothiazide alone.

It is concluded that both chlorothiazide and the mercurial diuretics lower the blood pressure in hypertensive patients but not in normal subjects. This effect is associated with a negative sodium balance, but at the same time the mechanism of this action is thought to be only partially dependent on sodium deprivation. To explain their results the authors suggest that there may well be suppression of some other arterial pressor mechanism.

A. E. Read

27. **Effect of Procaine, Carbocain and Xylocaine on Cutaneous Muscle in Rabbits and Mice.** [In English]

A. BRUN. *Acta anaesthesiologica Scandinavica* [*Acta anaesth. scand.*] **3**, 59–73, 1959. 10 figs., 10 refs.

The rabbit's skin was studied for its reaction to subcutaneous injection of procaine, xylocaine [lignocaine] and carbocain without adrenaline. The histological examination was extended to include an objective recording of the influence of the agent on the musculus cutaneus maximus by measurement of the diameters of the muscle fibres. These 3 local anaesthetics produced an essentially equally strong subcutaneous inflammatory reaction in concentrations between 0·5 and 2%, while a clear difference was found in the intracutaneous reaction. Xylocaine in concentrations 0·25 to 2% regularly produced inflammation and necrosis in the skin muscle. This reaction increased with the concentration of the agent tested. Two days after the injection of 1 to 2% xylocaine definite atrophy of the muscle fibres was demonstrable. Carbocain produced the same effect. Procaine (1 to 2%) produced no inflammatory irritation in the musculature and no muscular atrophy. An inflammatory reaction and degenerative changes in the skin musculature after the injection of xylocaine were also seen in mice.—[Author's summary.]

28. **Clinical Study of a New Synthetic Non-barbituric Hypnotic, 2-Methyl-3-*ortho*tolyl-4-quinazolone.** (Étude clinique d'un nouvel hypnotique de synthèse non barbiturique, la méthyl-2 *ortho*tolyl-3 quinazolone-4)
A. RAVINA. *Presse médicale* [*Presse méd.*] **67**, 891–892, May 2, 1959. 7 refs.

The sedative action of the non-barbituric compound 2-methyl-3-*ortho*tolyl-4-quinazolone (TR 495), a derivative of a synthetic antimalarial drug, has been studied in 100 patients who were given either 150 mg. orally or from 150 to 200 mg. rectally. In 20 cases the hypnotic effect was considered to be "excellent" and in 34 better than that obtained with other hypnotic drugs; in 28 the response was "fair", while in the remaining 18 it was unsatisfactory. In a few cases the drug showed evidence of synergistic action when combined with small doses of chlorpromazine or codeine, thus confirming the report by Cass and Frederik (*New Engl. J. Med.*, 1958, **259**, 1108; *Abstr. Wld Med.*, 1959, **25**, 393), who used it in association with codeine for suppression of pain. Side-effects were minimal, and no significant changes were observed in the peripheral blood count. TR 495 is considered to be a clinically useful new hypnotic.

Kenneth Gurling

29. **Mode of Action of Depolarizing Agents.** [In English]
P. B. SABAWALA and J. B. DILLON. *Acta anaesthesiologica Scandinavica* [*Acta anaesth. scand.*] **3**, 83–100, 1959. 9 figs., 44 refs.

It has been shown that with suitable doses of decamethonium, succinylcholine, or succinylmonocholine, a two-phase neuromuscular block can always be seen in isolated human intercostal muscle. The first phase consists of a neuromuscular block of rapid onset which reaches a maximum in about 15 minutes and then recovers spontaneously in spite of the continued presence of C_{10} in the same concentration. Recovery is maximum at approximately 60 minutes, after which time the second phase begins. The second phase consists of a slow, progressive neuromuscular block which reaches a steady reproducible state after 6 to 8 hours. If undisturbed, this state remains constant for hours. This phase represents a true competitive neuromuscular block, as evidenced by the fact that it can be reversed by a suitable dose of neostigmine.

Experiments have been described in which these two phases were modified by the addition of D-tubocurarine and neostigmine. Attempts are made to explain various phenomena on a molecular basis. The clinical significance of this work is presented.—[Authors' summary.]

30. **The Effect of Intravenously Administered Lidocaine and Succinylcholine on the Respiratory Activity of Dogs**
T. J. DEKORNFELD and J. E. STEINHAUS. *Anesthesia and Analgesia; Current Researches* [*Anesth. Analg. curr. Res.*] **38**, 173–177, May–June, 1959. 4 figs., 6 refs.

In an experimental study carried out at Wisconsin Medical School, Madison, adult mongrel dogs were anaesthetized with intravenous pentobarbitone and an endotracheal tube inserted; respiration, the electrocardiogram, and the electroencephalogram (EEG) were recorded throughout the study, during which the animals breathed room air. Suxamethonium in doses of 0·125 mg. per kg. body weight was then injected intravenously every 15 minutes and the duration of apnoea after each dose was noted in 6 dogs. The effects of repeated intravenous injection of lignocaine in doses of 10 mg. per kg. was similarly investigated. To 5 of the animals an initial dose of 0·125 mg. of suxamethonium per kg. was given and 10 minutes after apnoea had ceased 10 mg. of lignocaine per kg. was injected; after a further 10 minutes a second dose of 0·125 mg. of suxamethonium per kg. was administered and the duration of apnoea was again noted. After an interval of 45 minutes this series of injections was repeated in the same animals, the dose of suxamethonium being reduced to 0·0625 mg. per kg.

It was found that there was no significant change in the duration of apnoea following repeated doses of suxamethonium. Repeated injections of lignocaine produced transient respiratory depression up to the 6th dose, this last causing a short period of apnoea; the response returned to normal after a period of rest. When administered after suxamethonium lignocaine caused a moderate degree of respiratory depression and the succeeding dose of suxamethonium resulted in a more prolonged period of apnoea. It was noted that EEG activity was absent during the period of lignocaine apnoea. These findings are discussed in the light of other reported comparable studies. *Mark Swerdlow*

31. **A Study of Some Parasympatholytic and Parasympathomimetic Drugs**
M. SWERDLOW, J. MCCRACKEN, and J. MARKS. *Anesthesia and Analgesia; Current Researches* [*Anesth. Analg. curr. Res.*] **38**, 229–235, May–June, 1959. 3 figs., 4 refs.

In this study carried out at Salford Hospital Group, Manchester, a new atropine-like drug, Ro 1–7683, was compared with atropine, and a new anticholinesterase agent, Ro 1–5733, was compared with neostigmine. Four groups, each of 20 patients, received respectively: (1) atropine or Ro 1–7683, followed after 6 minutes by neostigmine; (2) neostigmine, followed after 6 minutes by atropine or Ro 1–7683; (3) atropine or Ro 1–7683, followed after 6 minutes by Ro 1–5733; or (4) Ro 1–5733, followed after 6 minutes by atropine or Ro 1–7683. All drugs were administered intravenously and in a dosage of 0·01 mg. per kg. body weight, except for Ro 1–7683 of which the dosage was 0·1 mg. per kg. Pulse rate and any symptomatic changes were noted 1, 3, and 5 minutes after the first injection and at regular intervals after the second injection.

It was found that atropine produced a significantly greater increase in heart rate than did Ro 1–7683. When given after neostigmine atropine produced a temporary increase in heart rate, whereas Ro 1–7683 did not. Ro 1–5733 produced a similar fall in heart rate to that caused by neostigmine and gave rise to similar parasympathomimetic symptoms. Ro 1–5733 in a dose of 0·005 mg. per kg. caused fewer symptoms of parasympathetic stimulation than did neostigmine in a dose of 0·01 mg. per kg.—[Authors' abstract.]

Chemotherapy

32. **Triclobisonium Chloride (Triburon), an Antimicrobial Agent with Local Activity in Living Host Tissues**
R. J. SCHNITZER, E. GRUNBERG, W. F. DELORENZO, and R. E. BAGDON. *Antibiotics and Chemotherapy* [*Antibiot. and Chemother.*] **9**, 267–276, May, 1959. 20 refs.

Triclobisonium chloride is a stable white crystalline solid readily soluble in water and alcohol. Chemically, it is a bisquaternary diamidine derived from β-ionone with surface-active and bactericidal properties. Triclobisonium chloride exhibits comparatively high antibacterial activity *in vitro*, particularly against pathogenic cocci, less so against *Escherichia coli* and *Pseudomonas aeruginosa*. Local lesions produced by subcutaneous injections of cultures of staphylococci or streptococci into the abdominal wall of mice could be prevented by infiltrating the area with triclobisonium solution immediately after the injection of the bacteria. The action against staphylococci *in vitro* was little affected by the presence of serum, but that against *E. coli* was reduced. Triclobisonium exhibits a moderate fungistatic activity against dermatophytes *in vitro*. The maximum oral or subcutaneous doses were ineffective against experimental intra-abdominal infections in mice with *Streptococcus pyogenes*, *Diplococcus pneumoniae*, and *Salmonella schottmülleri*; also against intravenously administered *Mycobacterium tuberculosis*, *Candida albicans*, and *Histoplasma capsulatum*. There was no activity against intranasal infection with influenza virus A or against the solid form of sarcoma 180 implanted subcutaneously. Little bacterial resistance to triclobisonium could be produced.

The authors conclude that the use of triclobisonium chloride as an antimicrobial agent for topical application is warranted. *Norval Taylor*

33. **The Clinical Side-effects of Antibiotic Therapy.** (Основные проявления побочного действия антибиотиков в клинике)
U. A. ASKAROV. *Терапевтический Архив* [*Ter. Arh.*] **31**, 32–43, July, 1959. 40 refs.

While most reports in the extensive literature on the side-effects caused by antibiotics have dealt with only a limited number of cases, the present author has investigated the incidence of such effects in a really large number of patients treated with these drugs. He reports that among 6,200 patients treated with penicillin and 1,200 treated with streptomycin allergic reactions occurred in 1% and 2% respectively and toxic reactions in 0·15% and 4·16% respectively. Chlortetracycline, chloramphenicol and "synthomycin" (a Soviet preparation of oxytetracycline) rarely caused allergic reactions, but toxic reactions were found to be fairly frequent, occurring in 21·8% of those given chlortetracycline and in 9·5% of those receiving synthomycin or chloramphenicol.

Haematological changes due to antibiotics mainly consisted in eosinophilia, and there was no evidence that any of the above antibiotics caused agranulocytosis; nor did examination of 6,000 cases reveal any history of thrombo-embolic complications, and the author therefore concludes that the antibiotics investigated have no appreciable influence upon the blood coagulation system. Although in the course of 15 years he has not seen a single case of septicaemia due to monilial infection, he recommends nevertheless that weakened patients be treated prophylactically with nystatin, vitamins, and iodine when, as in cases of severe infection, antibiotic treatment must be continued. The appearance of "microscopic" moniliasis of the mucous membranes ought not to prevent the use of antibiotic therapy when this is considered essential. *F. S. Freisinger*

34. **The Absorption and Excretion of Kanamycin in Human Beings**
G. A. CRONK and D. E. NAUMANN. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **53**, 888–895, June, 1959. 5 figs., 7 refs.

Kanamycin, a new antibiotic derived from *Streptomyces kanamyceticus*, is readily absorbed from parenteral sites. The peak concentration of kanamycin occurs at approximately one hour after administration, following which there is a rapid decline of serum concentration over the subsequent 12 hours. The average minimum serum concentration of antibiotic following the administration of 0·5 g. of kanamycin every 6 hours was 10 μg. per ml.; every 8 hours, 5 μg. per ml.; every 12 hours, 0·9 μg. per ml. The average high serum concentration of kanamycin was approximately 30 μg. per ml. regardless of the time interval between injections.

Approximately 90% of a given dose of kanamycin can be recovered in urine during the first 24 hours after injection with most of the total being excreted in the first 8 hours. The absorption and 24-hour excretion of kanamycin could not be influenced by bed rest, ambulation, fluids limited to 600 ml. per 24 hours or forced to 4,000 ml. per 24 hours.

Hyaline casts were more frequently observed in urine samples collected in the first 16 hours after the injection of kanamycin. All patients experienced mild discomfort at the injection site which did not interfere with further medication.—[Authors' summary.]

35. **Side-effects of Tetracycline Alone and of Tetracycline with Nystatin**
R. LARKIN. *Lancet* [*Lancet*] **1**, 1228–1229, June 13, 1959. 7 refs.

The simultaneous administration of nystatin with tetracycline inhibits the overgrowth of fungi in the intestines and has a similar, although less pronounced,

effect on yeasts in the throat. A total of 98 patients suffering mainly from acute or chronic respiratory-tract infections were divided at random into two groups, one group of 55 patients receiving 250 mg. of tetracycline hydrochloride 4 times a day and the other of 43 patients receiving in addition 250,000 units of nystatin 4 times daily.

Gastro-intestinal disturbances were noted in 37 of the 55 patients given tetracycline only and in 4 of the 43 given tetracycline with nystatin. Diarrhoea developed in 9 of the former group, but in none of the latter. On the fifth day of treatment yeasts were cultured from rectal swabs from 11 out of 19 patients treated with tetracycline and from 2 out of 18 given the tetracycline–nystatin combination. Thrush developed in the mouth in 3 of the 19 patients receiving tetracycline only, but was not observed in any of the 18 receiving nystatin and tetracycline.

It appears that nystatin not only affords protection against direct invasion of the tonsil by *Candida albicans*, which leads to clinical moniliasis, but it also substantially reduces gastro-intestinal disturbances during oral administration of tetracycline, which may be fungal hypersensitivity reactions.

[Recent reports suggest that nystatin is therapeutically effective in cases of chronic diarrhoea apparently due to moniliasis unconnected with administration of tetracycline.] *A. J. Karlish*

36. **Antiviral Action of Antibiotics Obtained from Cultures of *Actinomyces violaceus*.** (Противовирусное действие антибиотиков, продуцируемых культурами Actinomyces violaceus)
N. M. Furer, I. P. Fomina, O. I. Artamonova, and T. I. Balezina. *Антибиотики* [*Antibiotiki*] **4**, 30–35, May–June, 1959. 2 figs., 10 refs.

The authors have extracted from two strains of *Actinomyces violaceus* (Strains 1 and 719, isolated respectively from the soil of the left bank of the Volga and in Armenia), two substances which they term M–II and 719 and which have been found *in vitro* to exert a suppressive action upon the virus of influenza (Strains A, A1, and A2), the degree of inactivation of the virus depending on the concentration of the antibiotic and on the contact temperature. These preparations are both powders of a dark red colour, almost insoluble in water, but readily soluble in a 5 to 10% mixture of water and ethyl alcohol at *p*H 6·8 or 6·9. These two strains differ from Strain 1212, the source of "violarin", in not assimilating mannitol or sorbitol.

In the tests of antiviral action a suspension of influenza virus was mixed with equal volumes of these antibiotics in varying concentrations and incubated for 2½ hours at 4°, 24°, and 37° C. Each mixture was then diluted 100 times and 0·2 ml. injected into the allantoic sac of 10-day chick embryos which, after 48 hours' incubation at 37° C., were frozen and the allantoic fluid subjected to a haemagglutination test against chick erythrocytes. At a concentration of 2 to 5 mg. per ml. in the first incubation at 37° C. the haemagglutination titre fell from between 1,100 and 2,500 in the controls to between 40 and 80. In this test Preparation 719 was the more effective of the two substances. In a further study the effect of the nasal instillation of a suspension of virus incubated with 719 in a concentration of 2·5 mg. per ml. as described above was compared with that of the same viral suspension alone given respectively to two groups each of 10 white mice. Out of the animals in the former group, 7 survived, whereas only one out of the 10 controls did so. When the concentration of 719 was increased to 3·5 mg. per ml. 8 out of 9 animals survived.

A similar test with M–II resulted in no significant difference in the mortality of the two groups of mice, but there was a marked lessening of haemorrhagic changes in the lungs of the former group. The injection of 0·2 ml. of virus with an equal volume of antibiotic (about 0·3 mg.) completely suppressed the development of virus in the allantoic sacs of chick embryos, even when the dose of virus was 10,000 times the minimum infective dose, provided the antibiotic was given simultaneously with or up to 24 hours before the virus. If administered after the injection of virus it was effective only if given within 3 hours.

Lastly, in toxicity experiments on mice it was shown that both preparations were very toxic. The maximum dose of M–II tolerated was 10 mg. per kg. body weight when given subcutaneously and 2·5 mg. per kg. given intramuscularly, while 719 was 3 to 5 times more toxic, doses of 3 mg. per kg. instilled nasally and 0·5 mg. per kg. injected intramuscularly being the upper limits of toleration. At this dosage level the antibiotics had no effect upon the mortality of mice infected with influenza Types A and A2; the growth of the virus in the lungs, however, was delayed. It is possible that further research and purification of the preparations may, by lowering toxicity, enable them to be of therapeutic value in the treatment of viral influenza.

L. Firman-Edwards

37. ***In vitro* Studies on Increased Antibacterial Activity of Neomycin in the Presence of Certain Steroids**
J. R. Wilkins. *Antibiotics and Chemotherapy* [*Antibiot. and Chemother.*] **9**, 464–469, Aug., 1959. 1 fig., 14 refs.

A study is reported of the ability of the 21-acetates, 21-alcohols, and 21-sodium hemisuccinates of cortisone, hydrocortisone, and prednisolone to potentiate the antibacterial activity of neomycin against certain strains of *Staphylococcus aureus* and *Streptococcus haemolyticus*. Suspensions of the alcohols and acetates and aqueous solutions of the sodium hemisuccinates were used. It was found that 2 mg. of either steroid alcohol or steroid sodium hemisuccinate per ml. decreased the amount of neomycin needed to inhibit staphylococci (0·19 μg. of neomycin per ml.) and streptococci (6·2 to 12·5 μg. of neomycin per ml.) 10 to 50 times. The steroid acetates were ineffective. The addition of hydrocortisone sodium hemisuccinate (3·3 mg. per ml.) to a bacteriostatic amount of neomycin (1·0 μg. per ml.) produced a bactericidal effect. Hydrocortisone sodium hemisuccinate (2 to 3 mg. per ml.) alone temporarily suppressed the growth *in vitro* of *Staph. aureus*.

J. E. Page

Infectious Diseases

38. **Treatment of Shigellosis with Tetracycline in Infants under 2 Years of Age**
J. A. DE LA TORRE, J. OLARTE, and A. JOACHIN. *Pediatrics* [*Pediatrics*] **23**, 1136–1142, June, 1959. 14 refs.

The authors have attempted to assess the value of tetracycline in the treatment of children admitted to the Children's Hospital, Mexico, with bacteriologically proved shigellosis. A total of 98 children under 2 years of age were observed for a period of 60 hours, during which symptomatic treatment was given, including intravenous administration of fluids. The patients then received by random allocation either a placebo or tetracycline in a dosage of 50 mg. per kg. body weight every 24 hours, this treatment being continued for 7 to 8 days, or longer if necessary. Of the 98 patients, 28 recovered and 11 died during the first 60 hours; of the remaining 59 patients, 26 received tetracycline and 33 served as controls. Clinical cure was obtained in 14 of those given tetracycline and in 11 of the controls, the difference being of " doubtful significance ". The authors state that the proportion of recoveries with tetracycline was much smaller than that obtained by other workers, but that " the severity of the illness, the chronic course, and malnutrition should be taken into account among causes to which the high number of failures may be attributed ". *Norval Taylor*

39. **Local Factors in the Pathogenesis of Circulatory Failure in Diphtheria**
S. C. AGARWAL and L. B. HOLT. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **77**, 381–388, 1959. 5 figs., 6 refs.

Although it is generally recognized that the precipitating cause of death from diphtheria is circulatory failure, the precise mode of action of diphtheria toxin on the circulatory organs remains entirely unknown. The present investigation was undertaken at St. Mary's Hospital Medical School, London, in an attempt to analyse the local vasodilator action of diphtheria toxin.

The Schick reaction represents a direct vasodilator effect of diphtheria toxin in the skin, and microscopical examination of the fully developed lesion shows necrosis of surface epithelium, extravasation of neutrophil granulocytes, some hyaline thrombosis of the capillaries between the superficial and deep plexuses, and haemorrhages near the panniculus. When adrenaline or noradrenaline in a dose of 0·001 μg. contained in 0·2 ml. was injected into an area of the skin of an albino guinea-pig in which a positive Schick reaction had been produced by the previous injection of toxin the vasodilatation remained unaltered, whereas injection of the same dose into normal areas of the same guinea-pig's skin caused marked blanching. There are two possible interpretations of this finding—either the sympathomimetic effect of the drugs is interfered with by the toxin or the contractility of the smaller blood vessels is reduced or abolished. When larger doses of adrenaline were injected blanching was produced, but persisted for a shorter time than in normal skin.

The effect of diphtheria toxin on another smooth muscle with sympathetic innervation, the dilator of the rabbit's iris, was then studied. Injection of 1·25 guinea-pig MLD of diphtheria toxin into the anterior chamber produced a slight constriction of the pupil after 48 to 72 hours, but no gross inflammatory changes. The reactions of the pupil to light and atropine remained normal, showing that the sphincter pupillae and its parasympathetic innervation are not affected by diphtheria toxin. However, when 20 μg. of adrenaline was injected into the eye there was very little dilatation of the pupil as compared with the effect of the same dose on the control eye. This interference with the action of adrenaline did not occur in rabbits actively immunized with diphtheria toxoid.

The results of these experiments do not indicate which of the two possible explanations of the vasodilator action of diphtheria toxin is the correct one, but they do demonstrate that it causes a reduced sensitivity of the blood vessels to adrenaline which may play a part in the pathogenesis of circulatory failure in diphtheria.
K. Zinnemann

40. **Leptospiral Meningitis**
R. S. DÍAZ-RIVERA, F. RAMOS-MORALES, A. F. BENENSON, H. E. HALL, and E. J. MARCHAND. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **103**, 886–896, June, 1959. 2 figs., 32 refs.

This report is based on a study of 235 cases of leptospirosis seen at San Juan City Hospital, Puerto Rico, with special reference to the salient clinical features and in particular the meningeal aspects of the disease. Of 40 of these cases studied in detail and examined by lumbar puncture, 21 showed signs of involvement of the central nervous system, but in the other 19 patients, including 12 anicteric and 7 icteric cases, there were no signs of meningitis.

The authors have found that in infections due to *Leptospira icterohaemorrhagiae* the clinical signs of meningitis may be masked by the intense myalgia which is usually present. In some of the present cases laboratory evidence of meningitis was obtained even when definite clinical symptoms were absent, and leptospirae may be isolated from otherwise normal cerebrospinal fluid (C.S.F.) if lumbar puncture is performed early in the course of the disease. The changes in the C.S.F. do not appear to have any prognostic value, but the most pronounced changes are generally encountered among severe cases of typical Weil's disease with severe renal failure; in such cases the onset of hypotension and coma are very serious prognostic signs. In other cases the meningeal manifestations may be the most dominant

feature, appearing either before the onset of icterus or even in non-jaundiced cases, and in the authors' words " these phenomena call for a refined diagnostic accuracy and an increased level of suspicion of the disease ". They stress that the anicteric form of leptospirosis is at times indistinguishable from other acute infectious diseases such as murine typhus, dengue, severe influenza without obvious signs of acute respiratory infection, acute rheumatic fever, or septic meningitis. The final diagnosis in such cases must depend on laboratory confirmation.

The examination of the C.S.F. in the light of the clinical picture may aid the diagnosis by revealing the presence of leptospirae. A bilirubin-tinged spinal fluid (xanthochromia) is of limited diagnostic value in Weil's disease, since a clear fluid is the rule even in the presence of a high serum bilirubin level. *Edward Hindle*

VIRUS DISEASES

41. Influenza C in a Naval Recruit Population

P. K. FRASER, L. A. HATCH, G. N. SHELL, and J. M. R. FORSTER. *Lancet* [*Lancet*] **1**, 1259–1260, June 20, 1959. 6 refs.

A study is reported of the serum complement-fixing antibody titre against influenza virus C in recruits, aged 15 to 16 years, joining a naval training establishment in the Portsmouth area between May and October, 1958. Specimens of serum were taken on entry and again 3 months later from 392 recruits and tested by complement-fixation against antigens of influenza viruses A, B, and C, adenovirus, the psittacosis–lymphogranuloma venereum group of viruses, and *Rickettsia burneti*, fourfold or greater rises in titre being considered significant. Out of 379 paired specimens tested, 269 were negative; in 65 (17%) there was a significant rise in titre against influenza virus C antigen; and in 6 of the latter group and in a further 45 paired specimens there was a significant rise against other antigens. Paired specimens of serum from 60 recruits who spent one month only at this centre and were then transferred to Suffolk were also tested. Of these, 51 were negative, 3 showed a significant rise against influenza virus C antigen, and 6 showed a significant rise against other antigens.

Of the 62 recruits whose serum showed a rise in titre against influenza virus C antigen, respiratory-tract infection developed in 26, and of 320 who were serologically negative, 94 had upper respiratory-tract infection. Most of the infections occurred in those who joined the establishment between May and July, 1958. The epidemic was virtually over by the end of July.

Joyce Wright

42. Poliomyelitis under One Year of Age

D. LEVY and W. FALK. *A.M.A. Journal of Diseases of Children* [*A.M.A. J. Dis. Child.*] **97**, 829–838, June, 1959.

The authors discuss the clinical and laboratory findings in 529 cases of poliomyelitis occurring in infants less than one year old and treated at Rambam Government Hospital, Haifa, during the 6 years 1950–6, such cases representing 28 to 43% of the total number treated in different years. The series comprised 25 infants less than 3 months old, 108 between 3 and 6 months old, and 396 older than 6 months. Paralysis of the spinal type was present in 65% of cases, of the spinal-bulbar type in 11%, and of various other types (some with encephalitis) in 13%, while 11% of patients had no apparent paralysis. Muscle weakness first appeared during the first 3 days of illness in 47·5% of the 473 paralytic cases, between the 4th and 6th days in 32·5%, between the 7th and 10th days in 10%, and after the 10th day in 2%, the time of onset not being definitely known in the remaining 8%. Signs of meningeal irritation were elicited in 41% of all cases and were possibly present in a further 6%.

The number of leucocytes in the cerebrospinal fluid (C.S.F.) was determined in 455 cases; it was normal (0 to 10 per c.mm.) in 17·5%, slightly or moderately increased (11 to 70 per c.mm.) in 36·5%, and markedly increased (71 to >150 per c.mm.) in 46%. The protein content of the C.S.F. was normal (<30 mg. per 100 ml.) in 43% of 450 cases, slightly or moderately increased (31 to 60 mg. per 100 ml.) in 52·5%, and markedly increased (61 to >80 mg. per 100 ml.) in 4·5%. No correlation could be established between the presence or absence of signs of meningeal irritation and the laboratory findings. There were 77 deaths, of which 11 occurred in paralytic cases of the spinal type; in 7 of these 11 death was caused by lung infection complicating paralysis of the intercostal muscles and diaphragm, while gastro-intestinal disturbance with electrolyte imbalance occurred in 3 others and was probably a contributory factor.

An analysis of the laboratory findings showed there to be no constant pattern associated with any of the different clinical types. It is noted, however, that in this series the findings in the C.S.F. " did not follow the established pattern of ' pleocytosis with normal protein content ' at the beginning of the disease and ' normal white blood cell count with an elevated protein content ' later in the disease ". Further observations on poliomyelitis in infants are necessary before the significance of this observation can be determined. *R. G. Meyer*

43. The Place of Intrathecal Hydrocortisone in the Treatment of Acute Poliomyelitis. (La place de l'hydrocortisone intra-rachidienne dans le traitement de la poliomyélite aiguë)

A. AKKOYUNLU and F. ATAY. *Archives françaises de pédiatrie* [*Arch. franç. Pédiat.*] **16**, 500–505, 1959. 7 refs.

Poliomyelitis is a rare disease in Turkey and non-paralytic cases are rarely recognized, particularly as serological tests are not normally performed in cases of aseptic meningitis. The authors then report that in the autumn of 1956 a 3-year-old boy was admitted to the Children's Hospital, Istanbul, with a few days' history of rapidly ascending flaccid paralysis. By the time of admission all four limbs as well as the muscles of deglutination and respiration were paralysed and his condition was rapidly deteriorating. It was decided to treat him with intrathecal hydrocortisone in addition to

standard measures [these are not specified]. Within 24 hours the disease was arrested and progressive improvement continued over the next month, including return of power to all paralysed muscles except those of the right leg. This improvement is attributed to the treatment schedule, which consisted in a daily intrathecal injection of 12·5 mg. of hydrocortisone for 7 days, followed by 7 days' rest, injections as before for 7 more days, then 2 days' rest, and finally 3 more daily injections.

As a result of this favourable experience 3 further patients, aged one, 3, and 6 years respectively, were treated for paralytic poliomyelitis by a similar regimen, starting on the 10th, 13th, and 7th days respectively of the disease. Partial regression of the paralysis in these cases followed over a period of several weeks. In the belief that this improvement was due to the treatment with hydrocortisone the authors speculate on possible modes of action of the hormone and recommend their method as being safe and useful.

[All four case histories are fully consistent with the natural history of the disease, and no acceptable evidence is presented that hydrocortisone influenced it in any way. There is ample evidence available from other sources that corticosteroids are of no value in the treatment of poliomyelitis.] *John Lorber*

44. **Statistical Study of the Treatment of Acute Infective Hepatitis with Prednisolone.** (Étude statistique du traitement des hépatites ictérigènes aiguës par la delta-hydrocortisone)
P. MAINGUET and J. CAROLI. *Semaine des hôpitaux de Paris* [*Sem. Hôp. Paris*] **35**, 1974–1986, June 12, 1959. 9 figs., 39 refs.

Of 150 cases of acute infective hepatitis seen by the authors, 60 were treated by the so-called classic methods, that is, bed rest, antibiotics, and intravenous infusions of glucose or laevulose, while the other 90 received delta-hydrocortisone (prednisolone) either by mouth or by intravenous injection. The initial daily dose ranged from 25 to 40 mg., depending on the patient's weight and the gravity of the clinical and biological signs. These daily doses were gradually reduced in the cases treated early, and the steroid was usually discontinued after 15 to 20 days. The total dose of prednisolone varied between 3·5 and 5 g. The treatment of more protracted cases of infective hepatitis lasted sometimes several weeks. The authors recommend for the intravenous infusion a dose of 100 to 150 mg. diluted in 2,000 ml. of a 5% glucose solution.

Comparison of the results of the two methods of treatment showed that prednisolone given in the first week of illness considerably reduced the duration of the icterus and also of the total illness. The urinary crisis started earlier and the results of various metabolic tests returned sooner to normal. The authors note, however, that for prolonged forms of acute infective hepatitis and those treated tardily treatment with prednisolone is less effective and more dangerous. For such cases, therefore, they prefer the old methods of treatment, such as repeated duodenal intubation and surgical drainage of the gall-bladder. Both methods of treatment failed equally frequently in the more serious forms of infective hepatitis. The authors mention certain precautions to be taken before embarking on steroid therapy. Thus cases in which lesions or ulcers in the gastro-intestinal tract are suspected should be examined radiologically and prednisolone, if given, should be combined with anti-ulcer treatment. Patients suffering from pulmonary tuberculosis should be treated in addition with antituberculous chemotherapeutic agents, while the blood coagulation and arterial tension should be checked periodically.
Franz Heimann

45. **The Treatment of Mumps Orchitis with Prednisone**
E. S. MONGAN. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **237**, 749–753, June, 1959.

The efficacy of prednisone in the treatment of mumps orchitis was studied in 30 patients at the William Beaumont Army Hospital, El Paso, Texas, a double-blind method being used. Symptomatic treatment only was given to 10 patients; the remaining patients selected at random received either 10 mg. of prednisone or 10 mg. of thiamine hydrochloride 4 times a day. Neither the patient nor the doctor knew which drug was being administered. The duration of pyrexia and of the stay in hospital were the same in all groups and there was no difference between the three groups in the response to treatment. *Winston Turner*

46. **Infectious Mononucleosis and the Rickettsioses.** (Mononucléose infectieuse et rickettsioses)
P. MICHON, P. GIROUD, P. ARMAND, A. LARCAN, and F. STREIFF. *Sang; biologie et pathologie* [*Sang*] **30**, 200–207, 1959. 22 refs.

The authors describe 5 cases of "glandular fever" occurring in patients aged 18 to 26 years in which a serological test for rickettsiosis gave a positive result. The signs and symptoms included iridocyclitis, rash, generalized lymphadenopathy, faucial angina, and enlarged spleen. In 2 cases the Paul–Bunnell reaction was negative, but in the other 3 the titre ranged from 1:112 to 1:640. The leucocyte counts in the 2 negative cases were respectively 20,000 per c.mm. (lymphocytes 20%, monocytes 7%), and 9,600 per c.mm. (lymphocytes 26%, monocytes 3%). In the positive cases the count ranged from 9,000 to 13,000 per c.mm., with lymphocytes up to 47% and monocytes up to 27%. None of the patients had been inoculated against typhus. The agglutination titres for rickettsiosis were as follows: epidemic typhus 1:320 (2 cases); Q fever 1:20 to 1:80 (3 cases); and murine typhus 1:160 in one case, which also gave a positive result (1:320) for the epidemic form. In 2 cases the titre for Q fever reverted to negative after 2½ months, as also did the test for epidemic typhus in another case. In 2 cases the tests were not repeated.

The authors incline to the view that neither the Paul–Bunnell test nor the clinical picture are specific for the disease known as infectious mononucleosis, but may be caused by various pathogenic agents, including rickettsial infection. They do not believe that the rickettsial titres represent an anamnestic effect.
I. M. Librach

Tuberculosis

DIAGNOSIS AND PROPHYLAXIS

47. **The Coombs Test for Tuberculosis.** (Der Tb-Coombstest)
L. Popp. *Zeitschrift für Immunitätsforschung und experimentelle Therapie* [*Z. Immun.-Forsch.*] **117**, 419–449, June, 1959. 4 figs., 18 refs.

Writing from the Brunswick State Medical Research Institute the author discusses the Coombs test, which he uses for the diagnosis of tuberculosis, having found the results to be more specific than those of the haemagglutination and haemolysis reactions, which in cases of active tuberculosis too often give a negative result. Of 620 samples of serum examined, one-third were taken from patients with known tuberculosis and two-thirds were sent to the laboratory for differential diagnostic purposes, the clinical data in the latter cases being collected later by questionary.

The results of the Coombs test are compared with those of the Middlebrook–Dubos haemagglutination method, the Middlebrook haemolysis reaction, and the complement-fixation test using the "Essen" antigen, statistical analysis being employed to evaluate the results of the antibody titres. The Coombs test results showed the presence of incomplete antibodies in the serum of nearly all the patients with active tuberculosis; in that of subjects with inactive tuberculous processes there was a decrease in the incomplete and an increase in the complete antibodies. In the author's opinion a good correlation [no correlation coefficient is given] can be established by indirect haemagglutination tests between the serology of the immune antibodies produced by blood cell antigens and the serology of tuberculosis.

Franz Heimann

48. **Vaccination against Tuberculosis with Nonliving Vaccines. I. The Problem and Its Historical Background.** [Review Article]
D. W. Weiss. *American Review of Respiratory Diseases* [*Amer. Rev. resp. Dis.*] **80**, 340–358, Sept., 1959. Bibliography.

49. **The Case against B.C.G.**
A. S. Anderson, L. B. Dickey, M. L. Durfee, S. M. Farber, L. S. Jordan, K. B. Jordan, E. Kupka, H. D. Lees, E. R. Levine, C. A. McKinley, M. S. Marshall, J. A. Myers, E. A. Stoesser, and H. C. Sweany. *British Medical Journal* [*Brit. med. J.*] **1**, 1423–1430, June 6, 1959. 47 refs.

The 17 American physicians who have collaborated in this critical review of the safety and efficacy of vaccination with B.C.G. as a method of preventing tuberculosis, point out that as good or better results in tuberculosis control have been reported in parts of the world where B.C.G. has not been given as in those where the vaccine has been widely used. [Environmental differences between communities make this kind of comparison unsound as evidence for or against the value of B.C.G. vaccination.]

In the U.S.A. the danger of tuberculous disease in young people is becoming progressively less, and tuberculosis is being eradicated from bovine herds without the use of B.C.G. [The authors do not mention that the latter aim is being achieved by the slaughter of tuberculin-positive animals; the situation is not analogous to that in man.] It is objected that mass vaccination destroys the value of the tuberculin test as a diagnostic and epidemiological agent. Moreover, most primary infections resolve without incident—it is therefore not worth while to substitute vaccination with B.C.G. for a natural primary infection with pathogenic tubercle bacilli. [Although in the majority of cases the primary infection resolves without danger to the patient, there is much evidence to suggest that in a disquietingly high proportion of the remainder dangerous disease develops as a result of the primary infection.]

The authors claim that clinical trials of B.C.G. vaccine have not been helpful in assessing its value because of failure to differentiate between the innocuous primary infiltration and serious "re-infection type" disease. [In several clinical trials of B.C.G. the serious nature of the disease arising in the tuberculin-negative control groups has in fact been adequately demonstrated.] They also assert that B.C.G. vaccines vary and that some may be potentially dangerous. [B.C.G. vaccination has now been used intensively and on a large scale for many years; in practice it has been found to be a safe procedure.]

[This review does not give a balanced appraisal of B.C.G. vaccination. The objections raised are familiar and are in the main discounted by authorities with practical experience of the vaccine. The safety and efficacy of B.C.G. vaccine has been amply demonstrated on numerous occasions.] *T. M. Pollock*

50. **"B.C.G. Sarcoidosis"**
P. Ellman and L. G. Andrews. *British Medical Journal* [*Brit. med. J.*] **1**, 1433–1435, June 6, 1959. 2 figs., 30 refs.

In December, 1950, a 14-year-old tuberculin-negative girl—a participant in the Medical Research Council's clinical trial of B.C.G.—was vaccinated with B.C.G. and subsequently radiographed and skin-tested at approximately annual intervals. Three months after vaccination she was observed to have become tuberculin-sensitive. She was still tuberculin-sensitive when tested in May, 1956, and at that time her chest radiograph was normal. When next tested in July, 1957, she was tuberculin-negative and the radiographic appearances in her

chest were compatible with the diagnosis of sarcoidosis. A liver biopsy confirmed this diagnosis. By September, 1958, her chest radiograph had become normal and she was once more tuberculin-sensitive.

The literature relating to the occurrence of sarcoidosis in B.C.G.-vaccinated persons is reviewed.

T. M. Pollock

EXTRA-RESPIRATORY TUBERCULOSIS

51. **Chemotherapy of Renal Tuberculosis: a Survey of Ten Years' Clinical Research with the Development of an Effective Antimicrobial Treatment**

E. HALKIER and J. MEYER. *Danish Medical Bulletin* [*Dan. med. Bull.*] **6**, 97–104, June, 1959. 9 refs.

The authors comment on the radical improvement in the prognosis for patients with tuberculous infection of the kidney since the advent of streptomycin and record the experience at the Finsen Institute, Copenhagen, in the treatment of renal tuberculosis from 1943 to 1959. It falls into three periods: (1) 1943–49, when conservative treatment without chemotherapy was usual; (2) 1949–54, when chemotherapy was started, but the number of drugs used and the length of the treatment was variable; and (3) 1954–9, when three antituberculous drugs were used concurrently.

The results were as follows. During Period 1 the urine became persistently negative for tubercle bacilli (T.B.) in only 18 out of 90 patients (20%); in the others the disease slowly progressed until death ensued, usually from uraemia. During Period 2 (132 patients) chemotherapy was given in the form of streptomycin alone in a few cases, or as dihydrostreptomycin, 1 g. daily for 3 months, together with PAS, 12 g. daily for 6 months. Later dihydrostreptomycin was given in a dosage of 1 g. daily for 2 months, then 1 g. twice a week for 4 months, with PAS in doses of 12 g. daily and isoniazid, 300 mg. daily for 6 months. On this regimen the urine became persistently negative for T.B. in 99 of the cases (75%) and temporarily negative in 21, while in 12 cases it was never free from T.B. The poorest results were seen in the very young and the very old and in patients with concomitant extra-urogenital tuberculosis. It was noted that in healed cases cavities often persisted in the kidneys, and indeed in some cases appeared to be larger than before treatment. The infecting organism developed drug resistance in 21 cases.

During Period 3, 90 patients have been followed, these including patients selected from the previous series (1949–54) and new patients seen since 1954, but only those who had had treatment with all three drugs (dihydrostreptomycin, isoniazid, and PAS) from the start and in whom the bacilli were still sensitive to these drugs were included. Of these 90 patients, 82 (91%) ceased passing T.B. in the urine, 78 of them after one course of treatment and 4 after two courses; the other 8 patients continued to pass T.B. in the urine. In 3 of these last patients who were suffering from painful unilateral kidney disease nephrectomy was performed; the remaining 5 of the 8 patients were temperamentally abnormal and it was believed that they did not take the drugs regularly.

The authors conclude that conservative treatment with chemotherapy, using the three drugs mentioned, is the treatment of choice for renal tuberculosis. Nephrectomy is usually required only for the removal of a painful, nun-functioning kidney. *Arthur Willcox*

52. **Relapses, Recurrences, and Manifestations of "Larval Encephalitis"—Voujitch–Ristitch Signs—During and After Treatment of Tuberculous Meningitis.** (Rechutes, récidives et manifestations de "l'encéphalite larvée"—signes de Voujitch–Ristitch—au cours et à la fin du traitement de la méningite tuberculeuse)

K. TODOROVITCH. *Bulletin de l'Académie nationale de médecine* [*Bull. Acad. nat. Méd.* (*Paris*)] **143**, 429–433, June, 1959. 9 refs.

The author [who has had exceptionally wide experience in the treatment of tuberculous meningitis] has treated at the Infectious Diseases Hospital, Belgrade, no fewer than 2,034 cases of the disease between 1947 and 1958. He found [as others have done] that recrudescences during treatment and relapses after apparent recovery were quite common when streptomycin was the only drug employed. Unfortunately even prolonged treatment with a combination of drugs failed to eliminate these mishaps. Among 1,250 cases treated since 1950 recrudescences were noted in 86 and relapses in 67 patients, 4 of these relapsing twice. The author considers that provided the diagnosis is made early and adequate and long-continued antibacterial treatment combined with steroid therapy is given some 80 to 90% of the patients may be expected to recover [no details, however, are given].

It is well recognized that in tuberculous meningitis the brain itself is involved. When the usual signs of encephalitis are present the diagnosis presents no particular difficulty, but such signs are occasionally obscure. The author, however, draws attention to certain signs which are not commonly described; these were first observed and reported in a variety of neurological disorders by two Yugoslav physicians, Voujitch and Ristitch. They are as follows: (1) In one-fifth of patients convalescent from tuberculous meningitis a radial deviation of the closed fist, usually unilateral, may be observed when the arm is held extended horizontally. (2) A narrowing of the palpebral fissures, not being due to lesions of the facial nerve or the orbicularis muscle, has been noted in 6% of cases. (3) Elevation of the eyebrows (usually bilateral) when the patient fixes his regard on a finger moved laterally in front of the face; this sign is present in 11% of cases and may persist for years. (4) Lack of automatic swinging of one arm while walking, suggestive of paralysis though none is present, has been noted in 20% of convalescents; there may also be failure of some other automatic movements. These signs, several of which may occur together in the same patient, have no aetiological or localizing value, but are taken to indicate the presence of a lesion in the grey matter. *John Lorber*

Venereal Diseases

53. **Antitreponemal Antibodies in Syphilis in Man Revealed by the Fluorescence Reaction.** (Anticorpi antitreponemici nella sifilide umana svelati con la reazione di fluorescenza)

S. CENSUALES and V. GAROFALO. *Rivista dell'Istituto sieroterapico italiano* [*Riv. Ist. sieroter. ital.*] **34**, 161–167, May–June [received Aug.], 1959. 18 refs.

The authors, writing from the Institute of Hygiene and Microbiology of the University of Palermo, briefly survey the literature on the fluorescent treponemal antibody (F.T.A.) test described by Deacon *et al.* (*Proc. Soc. exp. Biol.* (*N.Y.*), 1957, **96**, 477; *Abstr. Wld Med.*, 1958, **24**, 26). The technique, which the present authors modified only slightly, is briefly recapitulated. In reading the result treponemata which have reacted with a positive serum are recognizable by their greenish-yellow fluorescence, which is absent if the reaction is negative.

Of 100 sera examined by the F.T.A. test in parallel with the cardiolipin and the Reiter protein complement-fixation and the treponemal immobilization (T.P.I.) tests, 38 gave a positive result in all 4 tests, while 16 gave a positive result with the T.P.I. and F.T.A. tests only. Only 4 sera gave a positive cardiolipin test result and these were considered as biologically false positive reactions. One serum gave a reaction to the Reiter protein test only and one to the F.T.A. test only; 37 sera were negative by all the tests. Thus the F.T.A. test agreed with the T.P.I. test in all but one of 100 sera [no clinical details are given of the exceptional case]. The authors point out that the F.T.A. test is simpler, cheaper, and can be performed more quickly than the T.P.I. test, but the latter is easier to read and the result is quantitative.

F. Hillman

54. **Evaluation of Treatment of Acute Gonorrhea in the Male with Varying Dosage Schedules of Penicillin V Potassium**

J. R. THURMAN. *Antibiotic Medicine and Clinical Therapy* [*Antibiot. Med.*] **6**, 295–296, May, 1959. 1 ref.

Although a number of antibiotics known to be effective in the treatment of gonorrhoea in the male are readily available, the author considered the present investigation of the efficacy of potassium phenoxymethylpenicillin to be justified because of the very high blood levels attained within a short time when the drug is given by mouth. It has already been shown that 30 minutes after a dose of 250 mg. of potassium phenoxymethylpenicillin by mouth the blood level is three times higher than that achieved with 600,000 units of procaine benzylpenicillin given intramuscularly. However, the effective blood level of the former falls considerably faster than does that of procaine benzylpenicillin.

A group of 22 men with acute gonorrhoea received 500 mg. of potassium phenoxymethylpenicillin initially and 250 mg. every 6 hours thereafter until 1,500 mg. had been administered, while a group of 18 similar patients were given a single dose of 750 mg. of the antibiotic. Each patient was asked to note how soon the discharge and dysuria ceased. Of the 18 who received 750 mg., 12 were completely well clinically within 48 hours, 4 had partial relief, and 2 did not appear to benefit. Of the patients given 1,500 mg., 17 were well within 48 hours, 3 were improved, and 2 failed to respond.

No valid conclusions can be drawn from the results, but the author considers that the drug is probably as effective as most oral broad-spectrum antibiotics in the treatment of gonorrhoea in the male.

Douglas J. Campbell

55. **Identification of *Neisseria gonorrhoeae* by Means of Fluorescent Antibodies**

W. E. DEACON, W. L. PEACOCK, E. M. FREEMAN, and A. HARRIS. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol.* (*N.Y.*)] **101**, 322–325, June, 1959. 3 figs., 11 refs.

This paper from the Venereal Disease Research Laboratory, Communicable Disease Center, Chamblee, Georgia, describes an attempt to develop a technique for the identification of *Neisseria gonorrhoeae* in smears by means of fluorescent antibodies. Young (12- to 16-hour-old) cultures of gonococci were killed by exposure to 100° C. for 30 minutes, to 120° C. for 2½ hours, and to 3% formalin for 30 minutes. After washing with buffered saline and adjustment of the density the suspensions were preserved with 0·3% formalin. Antisera were prepared against them and against living gonococci by intravenous injection into rabbits. Slide agglutination tests with the various suspensions against the untreated and absorbed antisera confirmed Wilson's observations that some gonococci may be inagglutinable by homologous antisera (*J. Path. Bact.*, 1954, **68**, 495; *Abstr. Wld Med.*, 1955, **17**, 435). The factor responsible for this is destroyed by heating at 120° C., but not at 100° C., and is thought to be similar to the Vi antigen of *Salmonella typhi* or the K antigens (B type) of the *Escherichia* group. The authors propose to call it the GC–K(B) antigen.

Rabbit antiserum to gonococci killed by formalin was coupled to fluorescein *iso*thiocyanate and the complex was shown to react strongly with cultured gonococci and to gonococci in films of urethral exudate from patients. Strong cross-reactions were obtained with meningococci of Groups A and B and to a lesser extent with those of Group C and with *N. catarrhalis*. Absorption of the labelled antiserum with fresh or boiled Group-A meningococci abolished the cross-reaction, but left the fluorescence with gonococci in urethral smears unimpaired. It was noted that fluorescence was well developed when cultures of gonococci 12 to 16 hours old were tested with the conjugated antiserum, but was less marked with cultures that were 30 hours old, suggesting that the factor responsible is rapidly lost as the culture ages.

A. E. Wilkinson

Tropical Medicine

56. **Analysis of a Year's Outpatients at University College Hospital, Ibadan**
K. M. COBBAN. *Journal of Tropical Medicine and Hygiene* [*J. trop. Med. Hyg.*] **62**, 129–134, June, 1959.

In order to gain some indication of the causes of morbidity in the indigenous population of Nigeria the author has analysed the records of 32,700 patients attending the out-patient departments of University College Hospital, Ibadan, which serves an estimated population of some 700,000 persons. From this study the following specially interesting points emerge. Over 4,000 gynaecological and obstetric cases, 3,718 cases of malaria, 4,292 of respiratory disease, and 4,164 of digestive disorders headed the list, these constituting from 10 to 11% each of the total. Tuberculosis was found in 7% of patients, including 1,608 cases of pulmonary tuberculosis, 326 of " glandular " tuberculosis, and 201 of tuberculous disease of bones and joints, mainly of the spine. Cases of nutritional deficiencies accounted for 4%, occurring mainly in children in the age group 1–5. The probable survival rate of children beyond the age of 5 years was 446 per 1,000 live births. Peptic ulcer was diagnosed in 338 cases—but the true incidence is probably much higher—appendicitis in 40, hypertension in 156, and rheumatic heart disease in 39. Other conditions included 623 cases of diseases of the blood, 532 of venereal disease, 264 of diseases of the nervous system (including 113 cases of epilepsy), and 616 cases of mental disorder, mainly psychoneurosis; an anxiety state is almost an occupational disease among certain classes, such as teachers, clerks, and students.

[This valuable paper is too full of facts and figures to be adequately abstracted. Similar studies from other large hospitals in Africa would be of great interest.]

Clement C. Chesterman

57. **Anaemia in Kwashiorkor**
F. WALT. *Journal of Tropical Pediatrics* [*J. trop. Pediat.*] **5**, 3–9, June, 1959. 1 fig., 20 refs.

The two principal types of anaemia seen in patients with kwashiorkor are megaloblastic anaemia and normochromic normocytic anaemia. The author of this paper from McCord Zulu Hospital and the University of Natal, Durban, states that megaloblastosis is estimated to occur in 15 to 20% of patients with kwashiorkor. Both megaloblastosis and kwashiorkor are more common in the summer months. Thus of 35 patients with kwashiorkor, 6 out of 25 seen between November and March had megaloblastosis, whereas none of the 10 patients seen between April and June had megaloblastosis. Patients with kwashiorkor complicated by megaloblastosis are often acutely ill, the haemoglobin level varying from 2·5 to 5 g. per 100 ml. A crisis characterized by a fall of 3 to 4 g. of haemoglobin per 100 ml. may occur within 24 hours. Although the condition will respond to administration of folic acid, blood transfusion is necessary to save life.

Normochromic normocytic anaemia is common in all patients with kwashiorkor. The haemoglobin level varies from 7 to 10 g. per 100 ml. In spite of adequate treatment with vitamins and a high-protein diet and apparent recovery from kwashiorkor, the haemoglobin level is very slow to rise. Of 36 patients with kwashiorkor admitted to the McCord Zulu Hospital between November, 1957, and June, 1958, 9 died. Of the 27 survivors, 4 required blood transfusion and were therefore excluded from the study. In the remaining 23 patients the mean haemoglobin level on admission was 10·3 g. per 100 ml. Despite resolution of clinical signs within 28 days of the start of treatment the mean haemoglobin level fell to 9·2 g. per 100 ml. In 18 patients it was still below 11 g. per 100 ml. 28 days after the start of treatment; all had been given a high-protein diet, 9 having received protein supplements in addition. In all 23 cases the serum protein level rose rapidly with treatment from a mean of 4·1 g. per 100 ml. to 4·8 g. per 100 ml. after one week and 5·9 g. per 100 ml. by the fourteenth day.

R. R. Willcox

58. **A Comparative Study of Intradermal Tests and Stool Examination in Epidemiological Surveys on *Schistosomiasis mansoni***
J. PELLEGRINO, Z. BRENER, and J. M. P. MEMORIA. *American Journal of Tropical Medicine and Hygiene* [*Amer. J. trop. Med. Hyg.*] **8**, 307–311, May [received July], 1959. 2 figs., 13 refs.

At the National Institute of Epidemiology, Belo Horizonte, Brazil, the diagnostic value of a single standard stool examination for the detection of eggs of *Schistosoma mansoni* was compared with that of intradermal tests using cercarial and adult worm antigen, 454 children from a schistosomiatic endemic area and 558 military personnel likely to have had less frequent contact with infected water being examined. In the children the stool examination gave a positive result in 298 (66%) and the cercarial and adult worm antigen skin tests in 58 and 55% respectively. Surprisingly, of the 298 children with positive stools, the two skin tests were positive in only 67 and 65% respectively. Again, of 62 children in whom the skin test was positive but the stool test negative on first examination, further stool examinations showed 52 to be harbouring eggs. Of the adult military personnel, the stools were positive in only 24%, whereas 53 and 51% gave positive reactions to the skin tests with cercarial and adult worm antigens. Of the 174 with positive skin reactions but negative stools on first examination, subsequent stool examination was positive in 112 cases. A further 13 cases in this group gave either a positive result by rectal biopsy examination or had a known history of infection. In

a control group of 100 children and 100 adults living in a non-endemic area the intradermal tests were negative in 92 to 98%.

It is concluded that in any epidemiological survey in which stool examinations and/or intradermal tests are employed it is of great importance to consider the age distribution of the group, while other factors also, especially those related to local conditions, must be taken into account in assessing the results. The need for standardization of the intradermal test is stressed.

The authors recommend that these diagnostic methods be compared in other and different epidemiological circumstances. *O. D. Standen*

BACTERIAL DISEASES

59. **Acute Bacillary Dysentery in Cyprus: a Comparative Study of Treatment in 332 Cases**
P. J. TAYLOR. *British Medical Journal* [*Brit. med. J.*] **2**, 9–12, July 4, 1959. 1 fig., 16 refs.

In order to assess the value of various regimens hitherto employed in the treatment of bacillary dysentery the author carried out a comparative trial at the R.A.F. Hospital, Akrotiri, Cyprus, in which all male patients (332) admitted with acute bacillary dysentery during 1957 and 1958 were included, only those who had already received chemotherapy being excluded. If a *Shigella* organism was isolated from the stool the case was termed " proved bacillary dysentery ", and if a bacillary exudate only was found it was called " clinical bacillary dysentery ". Of the types of *Shigella* isolated (146 cases) *Sh. sonnei* was found in 49·3%, *Sh. flexneri* VI in 35·6%, *Sh. flexneri* I in 12·3%, *Sh. flexneri* III in 1·4%, and *Sh. boyd* D1 in 1·4%.

In 1957 (173 cases) alternate patients were given either phthalylsulphathiazole in a loading dose of 9 g. followed by 4 g. 5 times daily for 6 days or dummy tablets containing minute quantities of vitamins twice daily for 6 days. The 7th day was a rest day and then on the 8th to the 13th days stool specimens were examined daily. Of the 87 patients treated with the sulphonamide, 6 relapsed (6·9%), whereas of the 86 in the control group, 15 relapsed (17·4%). In the sulphonamide-treated group only one (3·3%) of 29 cases of " proved bacillary dysentery " relapsed, whereas of 35 in the control group, 7 (20%) relapsed. In the treated group 58 patients had " clinical bacillary dysentery ", of whom 5 (8·6%) relapsed as against 8 (15·6%) of 51 cases in the control group.

In 1958 (159 cases) alternate patients were given either phthalylsulphathiazole in the same dosage as before (80 cases) or a proprietary preparation, " streptotriad ", containing in each tablet 65 mg. of streptomycin, 100 mg. of sulphathiazole, 100 mg. of sulphadiazine, and 65 mg. of sulphamerazine, 3 such tablets being given three times daily for 6 days, a total of 3·51 g. of streptomycin and of 14·31 g. of soluble sulphonamide. As before, the 7th day after treatment was a rest day and then 6 consecutive daily specimens of stool were examined. The average duration of diarrhoea in the phthalylsulphathiazole-treated group was 3·45 days for the proved cases and 3·43 days for the cases of clinical dysentery, or 3·44 days for the whole group; in the streptotriad-treated group the average duration of diarrhoea was 2·84 days for the proved cases and 3·02 days for the clinical cases, or 2·95 days for the whole group; the difference between the groups is statistically significant. The former group included 45 cases of proved dysentery, of which 8·9% relapsed, and 35 cases of clinical dysentery, of which 8·6% relapsed (8·7% relapses for the whole group). In the streptotriad-treated group (79 cases) there were 37 cases of proved dysentery, of which 10·8% relapsed, and 42 cases of clinical dysentery, of which 4·8% relapsed (average 7·6% for the whole group). The difference between the two groups in respect of the relapse rates is not statistically significant for the proved cases or the total cases, but the average duration of diarrhoea was shorter in the former group by half a day. Streptotriad was also more acceptable to the patient and is cheaper than phthalylsulphathiazole.

P. T. Main

60. **Sulphonamides and Streptomycin in Bacillary Dysentery: a Controlled Trial**
J. FALIŠEVAC, Z. KOŠUTIČ, and M. GALINOVIC-WEISGLASS. *British Medical Journal* [*Brit. med. J.*] **2**, 12–13, July 4, 1959.

The authors describe a controlled trial carried out at the Hospital for Infectious Diseases, Zagreb, Yugoslavia, on 48 patients suffering from bacillary dysentery. No patient who had received specific treatment before admission was included. Three types of treatment were studied. The 12 patients in Group 1 were given " sulphatriad " in tablets each containing 185 mg. of sulphathiazole, 185 mg. of sulphadiazine, and 130 mg. of sulphamerazine. Adult patients received 2 tablets 6-hourly for 7 days, this dosage being suitably reduced for children. From the stools of these patients *Sh. flexneri* was isolated in 5 cases and *Sh. sonnei* in 5; no *Shigella* were found in the remaining 2 patients. The stools became normal in appearance between the 1st and 6th days of treatment in all except 2 cases, and bacteriologically negative after the 5th day, cases due to *Sh. flexneri* infection clearing up more quickly than those due to *Sh. sonnei*.

Group 2 consisted of 15 patients who were given " streptotriad ", each tablet containing 100 mg. of sulphathiazole, 100 mg. of sulphadiazine, and 65 mg. of sulphamerazine plus 65 mg. of streptomycin sulphate, in a dosage of 2 tablets 6-hourly for 4 days. The infection in 10 of these patients was due to *Sh. flexneri*, in 2 to *Sh. sonnei*, and in one to *Sh. schmitzii*; in 2 cases no pathogenic organisms could be isolated. In most cases the stools became normal in appearance on the 5th or 6th day, and they were bacteriologically negative after the first day in 7 out of the 10 Flexner infections and on the 3rd and 5th days respectively in a further 2; the 10th case required chloramphenicol. The 2 cases due to *Sh. sonnei* became negative on the 1st and 2nd days respectively and the case of *Sh. schmitzii* infection on the 3rd day. To Group 3 (21 patients) 500 mg. of streptomycin

sulphate in tablet form was given 6 hourly for 4 days. Of these cases, 13 were due to *Sh. flexneri*, 4 to *Sh. sonnei*, one to *Sh. etousae*, and 3 were bacteriologically negative. In 13 cases the stools became normal in appearance between the 3rd and 7th days and in 3 cases they were semi-solid when the patient was discharged from hospital. In 9 out of 13 Flexner infections the stools became bacteriologically negative between the 1st and 4th days, but 3 were still positive on the 5th, 6th, and 7th days respectively. The 4 cases due to Sonne infection were negative between the 3rd and 8th days and the case of *Sh. etousae* infection became negative on the 5th day.

In discussion the authors point out that bacteriological cure preceded clinical cure and that sulphonamides were effective in infections due to *Sh. flexneri*, but less so in those due to *Sh. sonnei*, which, however, responded rapidly to the combined sulphonamide–streptomycin preparation. Both types of infection responded better to the combined treatment than to a large dose of streptomycin alone. *P. T. Main*

61. **A Depot Lepromin Test and B.C.G. Vaccination**
J. A. K. Brown and M. M. Stone. *Lancet* [*Lancet*] **1**, 1260–1262, June 20, 1959. 4 figs., 11 refs.

This paper from the Uganda Leprosy Service deals with three problems connected with the lepromin test which cause concern to those using or wishing to use it. The authors describe an attempt, based on recent advances in the preparation and application of tuberculin, to overcome these by the use of a depot lepromin applied with Heaf's multipuncture apparatus. The depot lepromin is prepared in an oily medium by the method described for depot tuberculin by James and Pepys (*Lancet*, 1956, **1**, 602; *Abstr. Wld Med.*, 1956, **20**, 261). [The former reference is incorrectly cited in the original.—Editor.]

The first problem in lepromin testing is that the supply of antigen is limited by the number of suitable lepromatous cases, which is being steadily reduced by modern methods of treatment. The new method, however, requires only one-hundredth of the amount of lepromin used in the intracutaneous method, so that 1 g. of leproma biopsy material should suffice for 20,000 tests. The second problem is that ulceration is liable to occur in the strongest reactors (who are the least endangered by infection) after intracutaneous injection, while dilution of the antigen sufficiently to avoid ulceration renders the test too insensitive for the detection of weak reactors, whom it is most important to protect. This difficulty is overcome by use of the Heaf technique, which causes no ulceration. The third difficulty in lepromin testing is the need for repeated testing with different strengths and, when B.C.G. vaccination is undertaken, for retesting to confirm conversion. Experiments carried out by the authors, however, showed that by the new method a single test with 1:100 depot lepromin is probably adequate to identify the weak reactor, and that the depot lepromin persists in the skin sufficiently long to indicate the effect of subsequent B.C.G. vaccination in negative reactors.

With the solution of these problems the study of whole populations at risk and further investigations of the protective value of B.C.G. will become practicable, and the search among patients' children and contacts for those most likely to develop non-self-healing leprosy will be facilitated.

Full details of the experiments are given, and photographs reproduced showing typical reactions to the test by the intracutaneous and new methods.

[Though the numbers of subjects used in some cases were small, the planning and working out of the experiments are impressive. Work projected with an intermediate strength (1:50) of depot lepromin promises further progress. The method of preparation of depot lepromin is probably described in sufficient detail for the information of those already making standard lepromin. But it is not stated whether the new preparation could be made commercially or how it is preserved.] *K. W. Todd*

62. **Diethyl Dithiol*iso*phthalate (ETIP or "Etisul") in the Treatment of Leprosy: a Second Progress Report**
T. F. Davey. *Leprosy Review* [*Leprosy Rev.*] **30**, 141–152, July, 1959. 2 figs., 1 ref.

In an earlier investigation (*Leprosy Rev.*, 1959, **30**, 61; *Abstr. Wld Med.*, 1959, **26**, 144) it was found that diethyl dithiol*iso*phthalate (ETIP; "etisul") was of some value as an adjuvant to the standard treatment of leprosy; no toxic effects were observed in a series of 65 patients so treated. In the present paper from the Leprosy Service Research Unit, Uzuakoli, Nigeria, the author reports the results obtained with this drug in treating 133 patients. It was given in the form of a 75% cream, 3 to 6 ml. of which was massaged over a wide area of the body twice weekly. No dermatitis or other toxic reaction was noted. Progress was assessed from the clinical findings and the fall in the "bacterial index", which is based on the average of findings in stained smears from multiple sites. The author states that fragmentation of the bacilli in smears is a favourable prognostic sign, and that the time taken for the proportion of normal bacilli to fall by 50% or 100% can be used to compare the effect of different forms of therapy. By this criterion it was found that in all 9 cases in a pilot trial group and in 7 out of 10 severe cases treated with ETIP alone there was a decline of 50% in the proportion of normal bacilli in the first 3 months. A 2-month course of ETIP was given to 15 patients in whom the bacteriological findings remained positive after 3 to 4 years of dapsone (DDS) therapy. In 2 cases smears became negative within 2 months. When ETIP was given combined with increasing doses of DDS up to a maximum of 400 mg. daily to 24 lepromatous patients the results after 3 to 9 months were very satisfactory. Finally, a group of 15 patients received ETIP combined with "Ciba 1906" (DPT), which rapidly reaches maximum activity; DDS was also given from the start so that the maximum dosage of 400 mg. daily was reached after 3 months at a time when the effect of ETIP began to diminish. The results to date are very satisfactory, with morphological change in 50% of the bacilli in 11 of the 15 cases within a month. The author considers that ETIP is of most

value at the beginning of treatment—that is, while the dosage of standard drugs is being built up to a maximum.

William Hughes

PROTOZOAL DISEASES

63. **A New Phenanthroline-quinone for the Treatment of Amoebiasis**

M. ATHANASIADOU and G. K. DAIKOS. *Journal of Tropical Medicine and Hygiene* [*J. trop. Med. Hyg.*] 62, 135–137, June, 1959. 9 refs.

Various phenanthroline-quinone compounds have been tried in various parts of the world during the past 3 years, with varying results, in the treatment of amoebiasis. The present authors report the use of phenanthroline-quinone semicarbazone (11925, " endobex ") in the treatment of 7 patients with chronic amoebic colitis and 19 symptomless cyst-passers at the Alexandria Hospital, Athens. The drug was given by mouth in doses of 300 mg. daily for 8 days. All the patients with symptoms showed immediate clinical improvement and the stools became normal, this improvement being maintained until their discharge about 20 days later. The stools were invariably negative for cysts after the 3rd or 4th day of treatment, but no adequate follow-up after discharge was possible. The type of the disease found in Greece is mild, which may account for the fact that the response to the drug was more favourable than that reported by others. Nevertheless, the authors consider their results encouraging. The side-effects noted were negligible. *Clement C. Chesterman*

64. **The Treatment of Amebic Dysentery with Paromomycin. A Preliminary Report**

A. Z. SHAFEI. *Antibiotic Medicine and Clinical Therapy* [*Antibiot. Med.*] 6, 275–278, May, 1959. 4 refs.

In this paper from the University of Alexandria, Egypt, a clinical trial is reported of paromomycin in the treatment of amoebiasis. One group of 10 patients received 10 mg. per kg. body weight daily for 14 days, while a similar group received 20 mg. per kg. body weight for 7 days. Both groups included patients with acute dysentery and patients with a history of recurrent dysenteric episodes. There was prompt amelioration in both groups; diarrhoea ceased and stool culture became negative in 3 to 8 days. There was a relapse in 4 of the patients given 10 mg. per kg. body weight daily and in 3 of those given the more intensive course.

[The conclusion to be drawn from this small trial is that paromomycin may relieve the symptoms of acute amoebic dysentery, but will not eradicate the infection with any degree of certainty.] *L. G. Goodwin*

65. **Puromycin Alone or in Combination with Phthalylsulfathiazole in the Treatment of Intestinal Amebiasis**

A. Z. SHAFEI. *Antibiotic Medicine and Clinical Therapy* [*Antibiot. Med.*] 6, 279–282, May, 1959. 11 refs.

Puromycin, an antibiotic derived from the fermentation of *Streptomyces alboniger*, was given alone or in combination with phthalylsulphathiazole in the treatment of 24 patients with acute amoebic dysentery or a history of recurrent dysenteric episodes, and the results are described in this paper from the University of Alexandria, Egypt. All the patients received 1 g. of puromycin daily for 14 days and 12 of them received in addition 3 g. of phthalylsulphathiazole daily. One patient was intolerant to puromycin and treatment had to be withdrawn. In 23 patients there was " definite clinical amelioration ", which was more rapid in those given puromycin and the sulphonamide. Relapse occurred in 4 patients treated with puromycin alone and in 2 given puromycin and phthalylsulphathiazole. Puromycin had no effect in hepatic amoebiasis.

[These results are not impressive.] *L. G. Goodwin*

66. **The Hematological Findings, Serum Protein Pattern and Liver Function Tests in Acute Amebic Dysentery and Amebic Liver Abscess**

S. J. POWELL. *American Journal of Tropical Medicine and Hygiene* [*Amer. J. trop. Med. Hyg.*] 8, 331–336, May [received July], 1959. 33 refs.

In this paper from the University of Natal and the Amoebiasis Research Unit, Durban, a study is reported of the blood picture, the serum protein pattern, and liver function in 49 African males suffering from amoebic dysentery, 31 similar patients with amoebic liver abscess, and 50 healthy controls. In patients with amoebic dysentery the haemoglobin level, the erythrocyte sedimentation rate (E.S.R.), the serum bilirubin and alkaline-phosphatase levels, and zinc sulphate turbidity were seldom disturbed, but leucocytosis was common. The α-globulin level was raised, but the γ-globulin level was normal. Reduction in the serum albumin concentration was thought to be due to lack of absorption in severe dysentery. Anaemia, leucocytosis, and a raised E.S.R. were common in patients with liver abscess. The serum bilirubin level was not raised, the alkaline-phosphatase level varied, but zinc sulphate turbidity was markedly greater than normal. Both the α-globulin and the γ-globulin levels were increased. The results of the cephalin–cholesterol flocculation test were unreliable in these patients.

The author concludes that the changes in amoebic dysentery are consistent with disturbance of bowel function, while the changes in liver abscess are those due to liver dysfunction. *R. A. Neal*

67. **The Serum Protein Pattern, Liver Function Tests and Hematological Findings in the Differential Diagnosis of Amebic Liver Abscess**

S. J. POWELL. *American Journal of Tropical Medicine and Hygiene* [*Amer. J. trop. Med. Hyg.*] 8, 337–341, May [received July], 1959. 28 refs.

The blood picture, the serum protein pattern, and liver function were studied in African patients with cirrhosis of the liver, primary carcinoma of the liver, or right basal pneumonia, the findings being compared with those in patients suffering from amoebic liver abscess. It was concluded that although " the results indicated certain differences between these conditions, their value in the differential diagnosis was not great ".

R. A. Neal

Allergy

68. **Clinical and Therapeutic Study of a New Synthetic Corticoid, Hexadecadrol, in Allergic Diseases.** (Étude clinique et thérapeutique d'un nouveau corticoïde de synthèse, l'hexadécadrol, au cours des maladies allergiques)
R. WOLFROMM, P. LIACOPOULOS, and J. L. BINET. *Semaine des hôpitaux de Paris* [*Sem. Hôp. Paris*] **35**, 1730–1737, May 18, 1959. 5 figs., 14 refs.

The effect of hexadecadrol (16α-methyl-9α-fluoro-Δ-hydrocortisone) was compared with that of prednisone in 41 allergic subjects, of whom 32 were suffering from asthma, 7 from paroxysmal rhinitis, 5 from eczema, 3 from urticaria, and 2 from Quincke's oedema, 8 showing more than one of these conditions. Hexadecadrol in a daily dose of 0·5 to 4 mg. appeared to act more rapidly and was tolerated better than prednisone in doses 5 to 10 times greater. In 22 subjects side-reactions to the hexadecadrol developed, these consisting in an increase in weight of up to 3 kg. in 14 cases and from 4·5 to 7 kg. in 4, while insomnia and tachycardia were troublesome in 5 subjects and in 2 others there were psychic disturbances. From one of these last patients and from another who had gastric disturbances the drug had to be withheld. It is claimed that the plasma levels of neither sodium nor potassium are affected by hexadecadrol. The authors advise that the same precautions should be observed with hexadecadrol as with the other corticosteroids.
J. Pepys

69. **"Weed" Pollen in Great Britain.** [In English]
H. A. HYDE. *Acta allergologica* [*Acta allerg.* (*Kbh.*)] **13**, 186–209, 1959. 8 figs., 18 refs.

Allergy to weed pollen appears to be rare in Great Britain although some of the pollens, such as those of plantain, dock, sorrell, and nettle, are liberated in large quantities. Volumetric counts show that the numerical incidence of 11 other herbaceous (weed) pollens does not reach 3% of that of grass pollen. The quantitative annual incidence of most kinds of weed pollen varies much less than does the annual incidence of tree pollens. Volumetric counts also show that nettle pollen is numerically the most abundant; it is therefore more likely to cause allergic symptoms than any other weed pollen.
A. W. Frankland

70. **Continued Follow-up Investigation Concerning the Fate of 298 Asthmatic Children.** [In English]
E. RYSSING. *Acta paediatrica* [*Acta paediat.* (*Uppsala*)] **48**, 255–260, May, 1959. 3 figs., 5 refs.

The author reports from the Municipal Out-patient Clinic for Allergic Diseases in Children, Copenhagen, on the further follow-up of 298 asthmatic children first followed up by Flensborg (*Acta paediat.* (*Uppsala*), 1945, **33**, 5), 5 to 18 years after their admission to hospital. For the present investigation, 18 to 31 years after their stay in hospital, information was obtained from 281 of the 283 survivors. The patients were now all over 18 years of age. Whereas in 1944 only 5 (1·7%) had died from asthma, by 1957 there had been 10 (3·4%) deaths; 163 still had acute attacks of asthma in 1944, and in 1957 there were 165 with asthmatic symptoms. Whereas 120 had been free from attacks for more than one year in 1944, only 106 had been free for a year in 1957. Only 58 had remained symptom-free from 1944 to 1957, but 16 others had become symptom-free since 1944, making a total of 74 cases. Only 3 of these patients had been desensitized, so that the figures indicate the natural remission rate.

More detailed analysis showed that the younger a child was when he first became free from attacks, the more likely was he to remain so. Of the 165 patients who still had asthmatic symptoms, 135 were able to work full time, while 29 were unable to work full hours or did so with difficulty or lost time through sickness. The author concludes that in cases of childhood asthma the spontaneous cure rate after puberty is about 30% in the absence of specific treatment.
R. S. Bruce Pearson

71. **Respiratory Studies in Children. VII. A Longitudinal Study of the Lung Volumes in Asthmatic Children during Symptom-free Periods.** [In English]
S. KRAEPELIEN. *Acta paediatrica* [*Acta paediat.* (*Uppsala*)] **48**, 335–344, July, 1959. 3 figs., 12 refs.

The purpose of this investigation was to obtain an objective record of changes over a long period in the condition of asthmatic children who had shown abnormal lung volume even during symptom-free periods. The author selected for study 18 patients aged 6 to 12 years attending the Paediatric Clinic of Karolinska Sjukhuset, Stockholm, in whom the ratio of residual volume to total lung capacity was elevated during symptom-free periods. In the majority the ratio between functional residual capacity and total lung volume was also raised, indicating the presence of hyperinflation of the lungs even during ordinary respiration. In all cases lung volume was estimated a second time after 17 to 28 months and in 16 cases again after 43 to 51 months. During the time between the tests the children received ordinary medical treatment as required and were entirely free of symptoms at the time of each testing.

To assess the results regression lines for the lung volumes on the three different occasions were related to body height and compared with similar regression lines in healthy children. On the evidence of the distance between the lines a progression towards normal appeared to have occurred between the first, second, and third examinations. This impression was investigated by covariance analysis, which showed that the distances between the regression lines for all lung volumes and their ratios were statistically significant as between the first and second investigations and also in comparison with the lines for healthy children, with the exception of the

total lung capacity in the second investigation. However, between the results of the first and third examinations the differences observed were significant for all volumes and ratios. At the final examination the regression lines showed no significant differences from those of healthy children except in respect of the ratio of functional residual capacity to total lung volume.

The improvement in hyperinflation found during symptom-free periods over the period of 4 years is taken to indicate that the abnormality present in these children was due to bronchial narrowing of a reversible nature rather than to emphysema. The improvement in the test results was found to agree with the clinical condition of the children assessed on the basis of the frequency of attacks over the 4 years, which diminished progressively in 8 of the 18 children and was reduced in a further 7. It is suggested that the change in lung volume towards normal is a hopeful prognostic sign.

[This valuable contribution to the investigation of an important problem in asthma merits reading in the original.] *K. M. Hume*

72. **Gamma Globulin in the Management of Asthma Associated with Infection**

S. FRIEDLAENDER, A. S. FRIEDLAENDER, and L. WEINER. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **238**, 18–24, July, 1959. 14 refs.

It has been suggested that the prophylactic administration of pooled γ globulin is effective in the treatment of asthma associated with respiratory-tract infection. In this paper from Wayne State University College of Medicine, Detroit, the authors report a trial of γ globulin in the treatment of 15 children aged 3 to 11 years who gave a history of repeated attacks of asthma precipitated by infections of the upper respiratory tract. All the patients had been observed for at least one year, during which treatment had consisted in a controlled diet, environmental control of allergens, hyposensitization, and administration of bacterial vaccines. During this period a detailed record was kept of the incidence of attacks of asthma and of respiratory-tract infections.

The dosage of γ globulin varied between 0·05 and 0·2 ml. per kg. body weight intramuscularly every 2 weeks; at the end of 2 months the dosage was increased to at least 0·3 to 0·5 ml. every 3 weeks except in 2 patients who appeared to benefit from the smaller dose. Treatment was continued for 8 to 14 months. In 6 patients, including 2 receiving the lower dosage, there was a marked reduction in the frequency of infections and subsequent episodes of asthma, and in 2 others moderate improvement was noted. In 3 the benefit was doubtful, while in 4 there was no apparent improvement.

In 11 cases the protein fractions in the serum were studied before treatment by paper electrophoresis and assayed by the immunochemical method of Goodman *et al.* (*J. Lab. clin. Med.*, 1957, **49**, 151). In 2 cases the γ-globulin value by paper electrophoresis was low, and in these and 2 others the assay value was also low. These patients responded well (3) or moderately well (1) to treatment. In 2 cases the γ-globulin level was high. After treatment there was a rise in the β-globulin level in almost every case, an unexpected and unexplained finding; the γ-globulin level was raised in 6 cases and reduced in 3. The authors conclude that γ globulin may be effective in asthma when the serum level of this fraction is low before treatment.

[The results of this study are little more than suggestive, because the patients were in the age group in which spontaneous improvement commonly occurs. Comparison with a group matched for age and sex but given an inert substance instead of γ globulin would be valuable. The authors refer to two reported controlled studies; in one of these treatment with γ globulin was apparently effective in increasing resistance to respiratory-tract infections and in the other there was no significant difference between the treated and the control groups. The dosage of γ globulin in these reported studies was comparable to that given in the present investigation.] *R. S. Bruce Pearson*

73. **Spirometric Evaluation of a Water–Alcohol-soluble Theophylline (Elixophyllin) in Acetylcholine-induced Asthma**

D. E. FRANK. *Antibiotic Medicine and Clinical Therapy* [*Antibiot. Med.*] **6**, 338–342, June, 1959. 6 refs.

The author reports a trial in which the bronchodilator effect of an orally administered water–alcohol-soluble theophylline ("elixophyllin") was measured by pulmonary function tests in 13 adult asthmatic patients (12 women and one man aged 23 to 71 years) and compared with the improvement which resulted from the intravenous administration of aminophylline and hydroxypropyltheophylline. The duration of the asthma varied between 2 and 20 years. The 3-second timed vital capacity and the maximum breathing capacity were determined for each patient during a period of freedom from dyspnoea and repeated after the administration of one of the drugs, which were given in the following doses: 2½ oz. (70 ml.) of elixophyllin (containing 400 mg. of theophylline), 0·5 g. of aminophylline, and 200 mg. of hydroxypropyltheophylline. Acetylcholine was then administered by aerosol inhalation and the pulmonary function tests repeated so as to assess the prophylactic effect of the three bronchodilator drugs in preventing acetylcholine-induced asthma. On a later occasion the acetylcholine was administered first and the improvement following each of the three aminophylline drugs was measured by the pulmonary function tests.

Intravenous aminophylline was found to be prophylactically superior to the other two drugs, but this was thought to be due to the higher blood theophylline levels achieved, since the dosage was higher. The improvement in acetylcholine-induced asthma which followed the administration of the three aminophylline drugs was as great for elixophyllin as for intravenous aminophylline and greater than that produced by hydroxypropyltheophylline. Furthermore it was found to be as effective as 0·3 mg. of adrenaline administered subcutaneously in both the prophylactic and therapeutic trials. An alcohol placebo used in the same trial did not have any appreciable prophylactic or therapeutic value.

K. M. Hume

Nutrition and Metabolism

74. **Serum Cholesterol Response in Man to Oral Ingestion of Arachidonic Acid**

A. KEYS, J. T. ANDERSON, and F. GRANDE. *American Journal of Clinical Nutrition* [*Amer. J. clin. Nutr.*] **7**, 444–450, July–Aug., 1959. 2 figs., 16 refs.

It is known that the addition of various polyunsaturated fatty acids to the diet has the effect of lowering the serum cholesterol level. Arachidonic acid is believed to be the most active of the fatty acids in regard to " essentiality ", and it might therefore be expected to have the property of lowering the serum cholesterol level to a greater degree than other polyunsaturated fatty acids. In this study, reported from the University of Minnesota, a concentrate of arachidonic acid obtained from liver and brain tissue was prepared in the form of capsules each containing 0·5 g. of concentrate and not less than 0·25 g. of arachidonic acid. Similar capsules containing 0·5 g. of oleic acid, which has virtually no effect on the serum cholesterol level, were administered during control periods. The experimental subjects were 6 middle-aged men who were kept on a constant diet for 70 consecutive days, divided into 5 periods; during the 2nd period 3 of the men received a supplement of 8 g. of arachidonic acid concentrate, while the other 3 were given 8 g. of oleic acid daily, this procedure being then reversed in the 4th period. A control group of 3 men, comparable in regard to age, body weight, and serum cholesterol concentration, received the same basic diet together with the supplement of oleic acid during both the 2nd and the 4th periods. It was found that in the 6 men given the supplement of arachidonic acid the serum cholesterol level showed a slight decrease during the first 4 days of supplementation, but thereafter rose steadily, attaining peak levels during the second week after withdrawal of the supplement, the mean increase in cholesterol level being 24·4 mg. per 100 ml. above the control values. Analyses of serum total cholesterol and β-lipoprotein cholesterol showed that all the changes in the serum total cholesterol level were accounted for by the increase in cholesterol in the β-lipoprotein fraction of the serum.

These findings seem to be in conflict with previous observations on the effect of the addition of polyunsaturated fatty acids to the diet. In seeking for an explanation the authors recall that linoleic acid is the precursor of arachidonic acid in the body; therefore a surplus of exogenous arachidonic acid would spare the use of linoleic acid and thereby create a relative surplus of linoleic acid; this surplus of linoleic acid would then be synthesized in the liver into cholesterol for β-lipoprotein. Thus it is necessary to distinguish between (1) effects dependent on an increased synthesis of cholesterol in the liver, and (2) effects dependent on increased biliary secretion and increased faecal excretion of cholesterol and the steroids derived from it. *Joseph Parness*

75. **Results of Addition of Liothyronine to a Weight-reducing Regimen**

E. P. GELVIN, S. KENIGSBERG, and L. J. BOYD. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **170**, 1507–1512, July 25, 1959. 6 figs., 18 refs.

The efficacy of a D-amphetamine–amylobarbitone preparation in the treatment of obesity was compared with that of a combination of this preparation and liothyronine in 57 obese patients seen at the Obesity Clinic, New York Medical College, the double-blind technique being used. All the patients were taking a 1,000-Calorie diet and were observed for 8 weeks on each therapeutic regimen. A preliminary study established that 75 μg. per day was the safe therapeutic dose of liothyronine. In the first 8-week period the two therapeutic regimens produced the same weight changes. When the liothyronine combination was given in the second 8-week period the weight loss continued at the same rate. When, however, D-amphetamine–amylobarbitone was given in the second 8-week period there was no further weight loss. It is suggested that liothyronine may be of great help to those patients who cannot maintain an adequate weight loss while on a weight-reducing diet.

Liothyronine did not appear to have any effect on the pulse rate, blood pressure, or serum cholesterol level, and there were no symptoms of hypermetabolism, such as nervousness, palpitations, or tremors.

A. G. Mullins

76. **An Inborn Error of Lipid Metabolism**

J. A. BIGLER, R. F. MAIS, R. M. DOWBEN, and D. YI-YUNG HSIA. *Pediatrics* [*Pediatrics*] **23**, 644–661, April, 1959. 9 figs., 30 refs.

A new clinical syndrome occurring in 2 brothers, aged 9 and 5 years respectively, both of whom showed a gross disturbance of the plasma lipid levels, is described in this paper from the Children's Memorial Hospital and Northwestern University School of Medicine, Chicago. There was a marked increase in the plasma triglyceride and phospholipid levels, but relatively little increase in that of total cholesterol. Electrophoresis indicated a considerable increase in lipoprotein concentration in the α_2-globulin region. Both children had marked hepatomegaly, which had been first noted at the age of 6 months, and were physically and mentally retarded. No abnormality was found in either parent or in the 6 other sibs. The parents were second cousins.

The authors conclude that the patients were homozygous for a rare abnormal gene. *H. Harris*

77. **Water Diuresis and Steatorrhoea**

C. T. G. FLEAR, W. T. COOKE, and A. QUINTON. *Clinical Science* [*Clin. Sci.*] **18**, 137–146, May [received Sept.], 1959. 2 figs., 39 refs.

Gastroenterology

78. **Needle Biopsy of the Peritoneum. A Preliminary Report**

R. F. Donohoe, B. I. Shnider, and J. Gorman. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **103**, 739–745, May, 1959. 5 figs., 15 refs.

A preliminary report on the diagnostic use of needle biopsy of the peritoneum is presented from Georgetown University School of Medicine, Washington, D.C. The main indication for peritoneal biopsy was ascites due to infection or neoplasm; in none of the 14 patients studied had the diagnosis been confirmed by any other method. A Vim–Silverman needle was used, and the authors' technique of performing the biopsy is described. Adequate peritoneal tissue was obtained in 12 of the 14 cases and in 6 (50%) of these a specific diagnosis of malignancy was established on the basis of the histological findings (photomicrographs showing carcinomatous infiltration of the peritoneum are presented); it is noted that in 4 of these 6 cases examination of ascitic fluid had not revealed any evidence of malignant cells or cultural evidence of tuberculosis. In the other 6 cases normal peritoneal tissue was obtained. No complications due to the biopsy were observed in the series. The authors suggest that this method of diagnosis deserves further study in intra-abdominal disease.

I. McLean Baird

79. **The Choice of Anticholinergic Drugs in the Treatment of Functional Digestive Diseases**

L. M. Asher. *American Journal of Digestive Diseases* [*Amer. J. dig. Dis.*] **4**, 260–275, April, 1959. 4 figs., 20 refs.

In this clinical evaluation of different anticholinergic drugs, which was carried out at the Cedars of Lebanon Hospital, Los Angeles, on 115 patients with duodenal ulcer and 121 with "indigestion", constipation, or diarrhoea, 11 synthetic quaternary ammonium compounds and 3 preparations containing belladonna alkaloids were investigated, each patient acting as his own control. Some of these drugs were used in combination with phenobarbitone, and it was noted that this usually enhanced the potency without intensifying the side-effects.

"Piptal" (pipenzolate methobromide) was the most satisfactory drug in suppressing gastric secretion and motility in cases of peptic ulcer, and its side-effects were mild. Long-acting "pro-banthine" (propantheline bromide)—but not the ordinary form—also proved satisfactory. Of the belladonna preparations, "donnatal", which contains a small amount of phenobarbitone, appeared to be the most valuable. Patients with the "irritable bowel" syndrome did not respond well to potent anticholinergic drugs and often developed atony of the bowel. Such patients did better on the weaker drugs, especially in combination with a barbiturate.

R. Schneider

80. **The Association of Hiatus Hernia and Gastro-oesophageal Malignancy**

R. A. Adler and J. Rodriguez. *Journal of Thoracic Surgery* [*J. thorac. Surg.*] **37**, 553–569, May, 1959. 19 refs.

This paper from the University of Buffalo School of Medicine, Buffalo, N.Y., begins with a brief review of the conflicting ideas expressed in the literature concerning the association between oesophageal hiatus hernia and malignant lesions of the oesophagus and stomach. The authors add their own series of 22 cases to 190 collected from the English literature in which the two conditions were associated, the tumour being an adenocarcinoma in 104, a squamous growth in 31, and a sarcoma in 6, while in 71 cases details of the histology were not available. The authors' 22 cases were taken retrospectively from the records of two hospitals over an 11-year period in which 697 cases of gastric carcinoma, 121 of which were in the region of the cardia and the proximal 4 to 5 cm. of the stomach, and 302 of primary oesophageal carcinoma, 73 of which were in the lower third, were treated. In the same period 814 cases of hiatal hernia were seen, in 22 (2·5%) of which gastro-oesophageal malignancy was also present [although if the authors' own criteria of including only malignancy occurring in the lower third of the oesophagus is strictly applied the number of cases is reduced to 18, a coincidence of 2·2%]. Of the 121 cases of carcinoma of the cardia, hiatal hernia was present in 12 (9·9%), and of the 73 cases of carcinoma of the lower third of the oesophagus, hiatal hernia was present in 6 (8·2%), the combined incidence being 9·2%. Attention is specially drawn to the sex difference, 5·1% of male patients with carcinoma having hiatal hernia compared with only 0·9% of females, despite the fact that hiatal hernia was more common in the latter (505:309). Individual reports are given of the authors' 22 cases, and among the points noted is the fact that of the 9 oesophageal malignancies, 6 were squamous carcinomata, 2 were adenocarcinomata, and one a leiomyosarcoma. Of these 9 patients, 3 alone had a history suggestive of long-standing gastro-oesophageal reflux and only in 4 others was the hiatal hernia diagnosed before the malignancy.

It is suggested that the association of hiatal hernia and malignancy probably occurs more often than is at present realized owing to difficulties in diagnosis by radiologist, surgeon, and pathologist. The question of cause and effect is discussed, and chronic irritation of the squamous epithelium of the lower oesophagus in the form of oesophagitis with ulceration, leukoplakia, and food stasis is suggested as having a malignant potential similar to that seen in other chronic oesophageal lesions such as achalasia and old corrosive strictures. Theoretically, primary adenocarcinomatous changes may occur in an oesophagus lined by columnar epithelium either congenitally or by replacement of the squamous epithelium after its destruction by reflux oesophagitis.

Trauma by the diaphragmatic margins of the hiatus leading to the formation of " gastric-type " ulcers in the herniated stomach is considered to be a poor explanation for the association of gastric malignancy and hiatal hernia. The idea is put forward that a carcinoma in the region of the cardia may produce a hiatus hernia as a secondary phenomenon by stimulating muscle spasm and shortening of the oesophagus.

The authors conclude that although there is probably more than a chance association between gastro-oesophageal malignancy and hiatal hernia, more evidence is required to prove this, and a review in retrospect is not the best way of getting it.

[This paper gives some support to the extremely important concept that a hiatal hernia may lead to malignant change in its neighbourhood, a view now widely (and in the abstracter's opinion rightly) held by many surgeons. This view has important implications for both physicians and surgeons managing patients with chronic reflux oesophagitis—the oesophagoscope and biopsy forceps are obviously most important instruments both for the diagnosis and for the supervision of all patients with this disease. One further suggestion is worthy of mention when considering the cause-and-effect relationship of these conditions, namely, that a carcinoma in the immediate vicinity of the cardia may, by ruining its sphincteric mechanism, cause incompetence and gastric reflux which may be reflected in the symptoms of the patient and be demonstrable radiologically even without the more obvious signs of a carcinoma. Progression of such a lesion to a secondary hiatal hernia is probably more than just a theoretical possibility.]

R. H. F. Brain

OESOPHAGUS

81. **Steroid Treatment of Lye Burns of the Esophagus**
C. L. MILLER and R. O. Y. WARREN. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **170**, 1525–1527, July 25, 1959. 10 refs.

This paper from the Delaware Hospital, Wilmington, Delaware, describes how 13 young children aged 8 months to 3 years who had swallowed various amounts of a strong solution of sodium hydroxide (lye) were successfully treated with prednisone and antibiotics.

The authors' regimen of treatment was as follows. For the first 3 days clear fluids only were given by nasogastric tube, followed by a soft diet for 3 weeks. The administration of prednisone, 1 mg. per lb. (2·2 mg. per kg.) and tetracycline, 15 mg. per lb. (33 mg. per kg.) body weight daily, was begun immediately on admission. After 7 to 10 days oesophagoscopy was performed. If no burning of the oesophagus was seen chemotherapy was stopped at once and the steroid gradually withdrawn. If a burn was present, as it usually was, a barium swallow examination was carried out a week later, before beginning to reduce treatment. In all 13 cases in the series this examination showed that no stricture was present. Follow-up ranged from 1 month to 3½ years; during this period no subsequent strictures developed and there were no other complications.

The authors state that before cases of this type were treated by steroid therapy, which was introduced on the basis of experimental evidence in animals, 50 to 70% of such patients developed oesophageal stricture. They consider in retrospect that nasogastric intubation is probably unnecessary and may even cause undesirable additional irritation. Two of their young patients pulled out the tube, which was not replaced, and fared just as well without it. *M. Meredith Brown*

82. **The Oesophago-gastric Sphincter after Cardiomyotomy**
M. ATKINSON. *Thorax* [*Thorax*] **14**, 125–131, June, 1959. 6 figs., 19 refs.

The object of the experiments reported in this paper from the University of Leeds was to determine whether complete destruction of the lower oesophageal sphincter leads to gastro-oesophageal reflux. For this purpose 18 patients from various hospitals who had undergone Heller's cardiomyotomy one month to 9 years previously, selected so as to include a number with reflux and to exclude all with any suggestion of a hiatal hernia, were studied. To these were added 23 control subjects of comparable age and sex, selected from students, staff, and patients without gastro-intestinal disease. Intra-oesophageal and intragastric pressure were measured by means of a pair of open-ended polyethylene tubes [of unstated diameter] filled with water and connected to external capacitance manometers. The tubes were coupled together in such a way that the end of one tube lay 5 cm. below the end of the other, simultaneous records being made from them at the end of expiration. All subjects were studied fasting and lying on the right side so as to produce the maximum difference in pressure between the lower end of the oesophagus and the fundus of the stomach. The tubes were passed until the tips of both lay below the diaphragm and were then withdrawn in 1-cm. stages, the pressure being recorded for 15 seconds at each interval, 6 such records being made in each case. A zone of raised intraluminal pressure 1 to 4 cm. in length was observed at the oesophago-gastric sphincter, and the difference between the highest pressure recorded from this zone and the intragastric pressure was taken as " an estimate of the state of contraction or tone of the oesophago-gastric sphincter ".

In the control group the mean estimated sphincteric tone was 8·4 (range 4 to 16) mm. Hg. The individual findings for the 18 patients are given in some detail. The estimated sphincteric tone ranged from 0 to 7 mm. Hg. In 10 cases it was in the lower range of normal values and in 8 it was zero or virtually zero. Included among these 8 patients were 4 of the 5 with reflux, as judged from " the presence of pain or discomfort in the chest brought on or aggravated by bending forward or lying flat and acid tasting fluid rising into the mouth ". [There is no mention of the x-ray findings except that the residue after a barium swallow was small, and it is not stated whether or not the clinical diagnosis of reflux was confirmed radiologically.]

The conclusion reached is that the oesophago-gastric sphincter cannot be the sole mechanism preventing

reflux because there was no reflux in 3 cases in this series in which the sphincter had apparently been completely severed.

[A more orthodox statistical presentation separating intra-patient from inter-patient variability would have made the results more convincing. As reflux occurs after food during waves of raised intra gastric pressure, it is difficult to estimate the importance of a pressure barrier represented by the difference between intra-oesophageal pressure and the very low intragastric pressure found in a fasting patient lying on the right side and which, even then, is not consistently present.]

Denys Jennings

83. **Further Observations on the Gastro-oesophageal Junction**

B. CREAMER, G. K. HARRISON, and J. W. PIERCE. *Thorax* [*Thorax*] **14**, 132–137, June, 1959. 7 figs., 7 refs.

The " sphincteric area " of the oesophagus is a zone of high pressure about 3 cm. long at its lower end, demonstrable by manometry but with no radiological counterpart. The " pressure barrier ", which coincides with the point at which the barium swallow is held up, is a sharply localized point about the middle of this zone at which the negative pressure swing on inspiration changes to positive. The investigations reported in this paper from St. Thomas's Hospital Medical School, London, were designed to determine: (1) the anatomical location of the pressure barrier; (2) the mechanism whereby barium is held up at this point; and (3) the part, if any, played by this mechanism in preventing gastro-oesophageal reflux.

Combined cineradiology and pressure measurements were carried out on 2 patients in whom radio-opaque markers had been fixed at thoracotomy anteriorly and posteriorly at the margin of the diaphragmatic hiatus and along the crus and also on the lower gullet at the level of the peritoneal reflexion from the gullet on to the under surface of the diaphragm. It was demonstrated clearly that in both inspiration and expiration the pressure barrier corresponded with the hiatus. In 24 other patients the lower gullet was deliberately opened during the repair of a hiatus hernia. In 21 cases the transition from oesophageal to gastric mucosa occurred within 1 cm. of the apex of the peritoneal fold—that is, the point where the peritoneum covering the abdominal oesophagus changes direction to pass outwards over the under-surface of the diaphragm. This suggests that the abdominal gullet, which forms the lower half of the pressure zone, is normally lined by gastric mucosa. The length of the abdominal gullet was measured in 5 normal subjects and in the 2 patients mentioned above by means of a pressure-recording tube filled with mercury distal to the orifice, which was placed at the pressure barrier, the subject being supine and the fundus outlined with barium; the mean length by this method was 2·5 cm. (range 1·4 to 3·3 cm.). In the same subjects the length of the abdominal gullet was also measured as the distance between the hold-up of barium and the fundus during inspiration, the mean value being 2·0 cm. (range 1·4 to 3·2 cm.). The behaviour of the abdominal gullet was also studied by combined cineradiology and pressure measurements in 10 normal subjects. When barium was flowing through it continuously the gastric end gradually widened until it became funnel-shaped and the point of demarcation between gullet and fundus became unrecognizable. In inspiration and expiration the abdominal gullet closed before the abdominal pressure rose above the oesophageal, so that there was no reflux, and opened as the oesophageal pressure rose above the abdominal. The pressure gradient from oesophagus to stomach at opening and closing of the abdominal gullet was always the same in any one experiment. The authors emphasize the distinction between reflux due to an increase in intra-abdominal pressure and reflux due to increased intragastric pressure. The segment of the gullet lying within the abdomen will clearly collapse with a sudden rise in intra-abdominal pressure and thus prevent reflux, and the authors suggest that " this valvular action of the abdominal gullet is an important part of the anti-reflux mechanism ". They point out, however, that " a rise in intragastric above intra-abdominal pressure would overcome this mechanism unless the sphincteric area contracted as part of the stomach ". If the lumen of the abdominal gullet is obliterated only at the level of the hiatus the rest funnels out into the fundus, and " one of the actions of the sphincteric area would appear to be to convert this wide, funnel-shaped area into a narrow tube ", the mucosal folds then blocking the cardiac orifice.

[This is one of the best discussions of the problem which the abstracter can remember reading, and the first one in the English language to give the reader the main facts, though many of the difficulties which still worry Continental radiologists, and which are of practical importance in the diagnosis of early carcinoma, are not mentioned.]

Denys Jennings

LIVER AND GALL-BLADDER

84. **Wilson's Disease, Portal Hypertension and Intrahepatic Vascular Obstruction**

W. J. TAYLOR, F. C. JACKSON, and W. N. JENSEN. *New England Journal of Medicine* [*New Engl. J. Med.*] **260**, 1160–1164, June 4, 1959. 1 fig., 32 refs.

To determine the cause of the portal hypertension which has been shown to be a factor in the causation of splenomegaly in Wilson's disease (hepatolenticular degeneration) 4 young adults with classic manifestations of the disease, including marked splenomegaly, were studied at the Veterans Administration Hospital, Pittsburgh, by catheterization of the hepatic vein, splenic puncture, and other methods. In 3 cases liver function was relatively unimpaired, but in the fourth there were severe symptoms of hepatic failure. In the 3 patients without hepatic symptoms the wedged hepatic venous pressure was normal, whereas in the 2 cases in which it was measured the splenic-pulp pressure was increased. In the patient with hepatic failure the wedged hepatic venous pressure was increased; in this patient alone was the hepatic blood flow reduced and the sulphobromophthalein clearance much affected. Splenoportography was performed on the 2 patients with elevated

splenic-pulp and normal wedged hepatic venous pressures and provided no evidence of extraportal venous obstruction, though collateral veins were seen.

In a lengthy discussion the authors state their reasons for taking their findings as evidence that in Wilson's disease there is obstruction to portal venous blood flow, the obstruction being in the presinusoidal part of the hepatic circulation. *W. H. Horner Andrews*

85. **Biochemical, Blood Gas and Peripheral Circulatory Alterations in Hepatic Coma**
M. P. Tyor and H. O. Sieker. *American Journal of Medicine* [*Amer. J. Med.*] **27**, 50–59, July, 1959. 6 figs., 45 refs.

Cirrhotic patients in hepatic coma often show hyperpnoea, arterial oxygen unsaturation, peripheral vasodilatation, and azotaemia. Writing from Duke University School of Medicine, Durham, North Carolina, the authors suggest that these additional factors might contribute to hepatic coma and account for the often poor correlation between the depth of coma and the blood ammonia levels. In the study of 49 cirrhotic patients, all males, the level of arterial blood ammonia was, however, found to be more closely related than was that of peripheral venous blood to the level of consciousness in individual patients studied serially during an episode of coma. While respiratory alkalosis is often present in comatose patients, its degree does not account for some of the discrepancies in blood ammonia levels. The very variable arterial oxygen saturation was shown to depend on various processes affecting pulmonary circulation and ventilation. A severe degree of azotaemia usually associated with oliguria occurred only in fatal cases. It is concluded that none of the additional factors studied played any special part in the development of hepatic coma. *J. McMichael*

86. **The Clinical Significance of Blood Ammonia Levels in Laennec's Cirrhosis**
N. W. Chaikin and M. S. Konigsberg. *Gastroenterology* [*Gastroenterology*] **36**, 785–789, June, 1959. 5 refs.

In this study, undertaken at the Metropolitan Medical Center, New York, to determine the prognostic significance of raised blood ammonia levels in patients with portal cirrhosis, three groups of patients were studied: (1) 27 cirrhotic patients with normal blood ammonia levels, of whom half were treated with a low-protein (50 g. per 24 hours), high-carbohydrate diet; (2) 28 cirrhotic patients with raised blood ammonia levels but without neuropsychiatric complications, the majority of whom were also treated with a low-protein diet, vitamins, and in some cases glutamic acid; (3) 18 cirrhotics with elevated blood ammonia levels accompanied by hepatic coma or threatened coma, all of whom were given initially intravenous infusions of sodium potassium glutamate and 500 ml. of 5% glucose solution followed later by dietary protein restriction.

In the patients in Group 1 the ultimate prognosis was determined not by the restriction of dietary protein, which had little or no effect on blood ammonia levels, but rather by the state of the liver as assessed by routine liver function tests. Of those in Group 2, adherence to a low-protein diet produced a fall in blood ammonia levels in 21, and follow-up showed that 16 of these were able to maintain their improved clinical status, whereas the 5 patients allowed an unrestricted protein intake deteriorated and were all dead within 18 months; the 2 remaining patients in this group died soon after admission. Of the 18 patients with neuropsychiatric complications (Group 3), 7 died despite treatment; in the other 11 there was marked improvement in the neurological status, but in 6, in all of whom tests had shown gross derangement of the liver parenchyma, a progressive downhill course could not be prevented even though the blood ammonia level fell. The other 5 are still alive on a strict low-protein diet. The authors conclude that an elevated arterial blood ammonia level signifies a poor prognosis in patients with cirrhosis, and in such patients a regimen of low dietary protein intake should be instituted at once, since it can considerably improve the survival rate. Normal blood ammonia levels have no prognostic significance. *A. E. Read*

87. **Zinc Metabolism in Hepatic Dysfunction**
B. L. Vallee, W. E. C. Wacker, A. F. Bartholomay, and F. L. Hoch. *Annals of Internal Medicine* [*Ann. intern. Med.*] **50**, 1077–1091, May, 1959. 7 figs., 41 refs.

In investigations reported from Harvard Medical School and Peter Bent Brigham Hospital, Boston, the average concentration of zinc in the serum of 33 patients with post-alcoholic cirrhosis was found to be significantly lower than in 40 healthy control subjects. Thus the mean serum zinc content for the controls was 120 ± 19 μg. per 100 ml., that for 25 patients with severe cirrhosis 66 ± 19 μg. per 100 ml., and that for 8 patients with mild cirrhosis $87{\cdot}8\pm20$ μg. per 100 ml. The mean daily excretion of zinc in the urine was approximately twice as high in 9 patients with severe cirrhosis (1,030 μg.) as in 14 healthy controls (457 μg.). Liver samples obtained at necropsy from 5 patients with cirrhosis showed a significant decrease in zinc content compared with samples from 7 subjects with no histological evidence of liver disease. *H. Harris*

88. **Plasma Prothrombin in Liver Disease: Its Clinical and Prognostic Significance**
G. Mindrum and H. I. Glueck. *Annals of Internal Medicine* [*Ann. intern. Med.*] **50**, 1370–1384, June, 1959. 3 figs., 29 refs.

The TAMe [*p*-toluene sulphonyl-arginine methyl ester] assay of prothrombin utilizes a chemical method for specifically measuring plasma prothrombin. The assay is not influenced by deficiencies of accessory clotting factors, V and VII, or fibrinogen, which affect one-stage methods to a considerable degree.

The TAMe assay of prothrombin correlates well with the clinical status of the patient with liver disease. Extremely low levels were found in fatal cirrhosis or necrosis. Patients with severe cirrhosis had persistently low values for months or years, whereas cases of viral hepatitis showed higher values and more rapid changes. Serious or fatal liver disease showed little or no response

in the prothrombin assay after the administration of vitamin K_1 emulsion, in contrast to viral hepatitis, which showed prompt improvement. The true prothrombin levels invariably lag behind more rapidly recovering accessory factors.

Statistically, a good correlation exists between the TAMe assay and the albumin : globulin ratio, and an excellent statistical relationship is apparent between the TAMe assay and the "bromsulfalein" retention. The TAMe assay of plasma prothrombin may be employed in acute or chronic liver disease, and is not influenced by the degree of jaundice. Since the assay measures a specific product of the liver, it serves as a useful liver function test. Serial assays yield excellent prognostic information.—[Authors' summary.]

89. **Amino Acids in Arterial and Hepatic Venous Blood of Patients with Laennec's Cirrhosis**
S. M. MELLINKOFF, T. B. REYNOLDS, M. FRANKLAND, and M. GREIPEL. *Gastroenterology* [*Gastroenterology*] **36**, 780–784, June, 1959. 2 figs., 8 refs.

In a study of the role of the liver in the metabolism of amino-acids, carried out at the Universities of California and Southern California, Los Angeles, the amino-acid content of samples of blood from the femoral artery and the hepatic vein of 14 patients with portal cirrhosis was investigated by two-dimensional paper chromatography. The effects of vasopressin (which lowers hepatic blood flow) on the amino-acid pattern were also studied, while in one cirrhotic patient who had made a successful recovery from a portacaval shunt operation the pattern was studied after a milk feed. Two subjects with normal liver function were also similarly investigated, in one case immediately after the intravenous infusion of an aqueous solution of amino-acids.

The only fairly consistent change noted, and that not in all of the cirrhotic patients, was a fall in the α-alanine content and an increase in the glutamic acid level in the hepatic venous samples. Other changes occurred but were inconstant; the one patient with the shunt who was retested in the fasting state after a milk meal showed a rise in the previously low levels of some amino-acids in hepatic venous blood. The 2 subjects with normal liver function showed changes not unlike those in the cirrhotic patients, but in one patient with Korsakoff psychosis a very large increase in the venous blood glutamic acid level was noted. Vasopressin caused no alteration in the amino-acid pattern. In the normal subject given the infusion of amino-acids some of these acids were present in a higher concentration in the arterial than in the venous blood samples 45 minutes after the infusion had been started. The authors suggest that these results —which they assume to be valid for the hepatic artery as well as the femoral artery—confirm that the liver plays a part in amino-acid metabolism. The extraction of α-alanine by the liver and the production of glutamic acid have previously been noted in normal subjects. The precise stimulus leading to the alteration by the liver of amino-acid levels in the blood is unknown, but the authors suggest that the high glutamic acid concentration observed may be a protective mechanism, that is, an attempt to protect the brain from the toxic effects of ammonia by uniting with it to form harmless glutamine.

A. E. Read

LARGE INTESTINE

90. **The Liver in Ulcerative Disease of the Intestinal Tract: Functional and Anatomic Changes**
A. S. MONTO. *Annals of Internal Medicine* [*Ann. intern. Med.*] **50**, 1385–1394, June, 1959. 33 refs.

The author, working at New York Hospital–Cornell Medical Center, has studied 100 patients with ulcerative colitis and 50 with regional enteritis and the necropsy records in 100 cases of ulcerative colitis and 4 cases of regional enteritis with the object of defining the hepatic abnormalities which occur in these conditions. In the patients with ulcerative colitis the findings in the clinical cases and the post-mortem series were very similar. Some 20% of patients had hepatomegaly and 18% had some biochemical abnormality attributable to disturbed hepatic function. A prolonged prothrombin time and a reversed albumin:globulin ratio were not accepted as specific tests of liver function. [Similar reservations could be made about the other tests employed.] The commonest post-mortem abnormalities in the liver were fatty infiltration and chronic inflammatory changes. [Apparently no biopsy examinations were performed.] True cirrhosis was never found. The liver was palpable in 13 of the 50 patients with regional enteritis.

[The findings in this study are not well presented and the author does not make it clear whether he personally studied the patients and pathological sections or only the written records—one suspects the latter.]

P. C. Reynell

91. **Carcinoma and Ulcerative Colitis; a Clinical-pathologic Study. III. Survivors**
M. B. GOLDGRABER, E. M. HUMPHREYS, J. B. KIRSNER, and W. L. PALMER. *Gastroenterology* [*Gastroenterology*] **36**, 613–630, May, 1959. 15 figs., 17 refs.

In this third paper of a series on carcinoma and ulcerative colitis from the University of Chicago the authors describe in detail 9 cases in which the patient had survived operation for carcinoma of the colon complicating ulcerative colitis and was still alive. There were several points of difference from the ordinary case of carcinoma of the colon: (1) the age when the carcinoma was diagnosed was much earlier, averaging 37 years (range 19 to 68 years); (2) the carcinomata were more evenly spread throughout the colon, including the appendix; (3) the tumours were multiple in 4 and possibly 5 cases, while pseudopolyps were common, being present in 7 cases and appearing to undergo malignant changes; and (4) the histological picture was much wider, varying from a poorly differentiated adenocarcinoma with extensive infiltration to a highly differentiated adenocarcinoma. At the time of diagnosis of the carcinoma the average duration of the colitis was 11 years. Although exfoliative cytology is difficult in these cases, malignant cells were definitely seen in 2 cases. Lymph-node involvement did not appear to exclude a long survival.

A. Gordon Beckett

Cardiovascular System

92. **Lipid Studies in Health and Disease: Preliminary Report of the Results of Lipid Determinations in a Group of Normal Officers and Patients with Vascular Diseases**
T. W. MATTINGLY, L. F. PARMLEY, E. L. DURRUM, E. R. B. SMITH, and M. R. HYATT. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **170**, 536–541, May 30, 1959. 3 figs., 18 refs.

An investigation was carried out at the Walter Reed Army Hospital and Institute of Research, Washington, D.C., into the value of determinations of serum lipid levels in the diagnosis and prognosis of atherosclerosis. Three groups of 100 male officers, aged 25 to 34, 35 to 44, and 45 to 59 years respectively, with no history or clinical, electrocardiographic, or radiological signs of cardiovascular disease were first studied as controls. The mean serum cholesterol value in the group aged 35 to 44 was significantly higher than in that aged 25 to 34, but did not differ significantly from that in the group aged 45 to 59. The differences in the serum lipoprotein values between the age groups were not significant. The mean values for the whole group of 300 were then compared with those of (1) 200 consecutive patients suffering from proved myocardial infarction, (2) 100 with angina pectoris not complicated by manifest myocardial infarction, (3) 75 with arteriosclerosis obliterans and intermittent claudication, and (4) 100 suffering from severe hypertension but without clinical evidence of coronary disease.

In Groups 1 and 2 the mean values for cholesterol and lipoproteins (both the S_f 12–20 and S_f 20–100 fractions) were significantly increased. In Group 3 the cholesterol and S_f 12–20 lipoprotein values were increased, but the S_f 20–100 lipoprotein level was normal. A similar increase in the cholesterol and S_f 12–20 lipoprotein levels was found in Group 4, but the increases were less than those in Group 3, which in turn were less than in Groups 1 and 2. However, individual variations within each group were great and the differences between the values for normal and diseased persons were comparatively small, " thus preventing efficient application of the clinical theory of identification and prediction of atherosclerosis ".

The authors conclude from these studies that measurement of the serum cholesterol level is more useful in detecting disturbances of lipid metabolism which may be associated with atherosclerosis or a predisposition to it than the more complicated determination of lipoprotein values. They suggest that if the serum cholesterol level is significantly increased in an otherwise normal young adult man a search should be made for further evidence of premature vascular disease. *Z. A. Leitner*

93. **Hypothermia.** [Review Article]
L. D. VANDAM and T. K. BURNAP. *New England Journal of Medicine* [*New Engl. J. Med.*] **261**, 456–553, Sept. 10, 1959, and 595–603, Sept. 17, 1959. Bibliography.

94. **Temperature Gradients during Hypothermia**
V. HERCUS, D. COHEN, and A. C. BOWRING. *British Medical Journal* [*Brit. med. J.*] **1**, 1439–1441, June 6, 1959. 2 figs., 8 refs.

Since the temperatures recorded in various parts of the body during hypothermia do not always correspond the authors carried out experiments in animals designed to compare the temperature at different sites. They registered with accurate thermistor recorders changes occurring in the cerebral cortex, heart, oesophagus, rectum, nasopharynx, and subcutaneous tissues, these recordings being obtained while the animal was being cooled in a bath down to 29° C. and again on rewarming. It was found that the temperature in the lower third of the oesophagus corresponded closely to that of the cerebral cortex. The blood stream temperature was below that of the brain during cooling and above it during warming. Rectal and nasopharyngeal temperatures followed the general pattern, but more slowly.

It is concluded that the lower third of the oesophagus is the logical site from which to record the body temperature since here it is almost identical with the temperature in the cerebral cortex. *T. Holmes Sellors*

95. **Controlled Hypothermia in Infants and Children**
D. COHEN and V. HERCUS. *British Medical Journal* [*Brit. med. J.*] **1**, 1435–1439, June 6, 1959. 4 figs., 16 refs.

The value of hypothermia in cardiac surgery in children is now established. In this paper from the Congenital Heart Disease Unit, Royal Alexandra Hospital for Children, Sydney, the authors discuss the most satisfactory ways in which a reduction of body temperature to 30° C. can be obtained and controlled and then describe their own method, which is as follows. The child is placed on the operating table and enveloped in blankets through which water can be circulated. The temperature is controlled by water circulation from tanks which can be cooled or warmed as required. In addition to blankets a neck coil is used. The operation is started while the temperature is being lowered, and when the appropriate level has been reached the degree of cooling is stabilized and held until the necessary part of the operation has been completed. Rewarming is carried out by circulating hot water through the blankets.

This method has been used in some 50 patients operated on for a variety of conditions, including atrial septal defect, pulmonary stenosis, and a number of other congenital lesions. The authors consider that patients with coarctation of the aorta should be operated on under hypothermia because of the greater ease of technical performance and the lessened risk of spinal artery thrombosis. The results have proved satisfactory and abnormalities in cardiac rhythm have not been encountered.
T. Holmes Sellors

96. **Thyroid Function in Circulatory Insufficiency.** (О функции щитовидной железы при недостаточности кровообращения)
A. Z. Cfasman. *Клиническая Медицина* [*Klin. Med. (Mosk.)*] **37**, 76–81, June, 1959. 2 figs., 26 refs.

Both thyroidectomy and administration of thyroid extract have been recommended at various times for the treatment of cardiovascular diseases. The estimation of thyroid function in these conditions, however, is difficult. Determinations of the basal metabolic rate and of the amount of radioactive iodine (^{131}I) retained by the thyroid gland are unreliable in view of the increased work being performed by the respiratory musculature and myocardium and the abnormal extra-thyroid metabolism of ^{131}I. In the present studies, carried out at the Central Postgraduate Institute, Moscow, the ^{131}I clearance test was therefore used. This test consists in estimation of the amount of ^{131}I retained by the gland in any one minute and of the blood concentration of ^{131}I in the same minute; in this way the extra-thyroid metabolism of iodine does not influence the result. The subjects were 62 patients (27 male and 35 female ranging in age from 17 to 64) with cardiac insufficiency of varying degree and of the following aetiologies: rheumatic, 55 cases; syphilitic, 1; congenital, 1; pulmonary, 4; and atherosclerotic, 1. The values for clearance of ^{131}I were normal in all but 5 patients, of whom 2 showed some increase and 3 a slight diminution. Both the patients with increased clearance showed clinical evidence of thyrotoxicosis, while signs of hypothyroidism were found in only one with diminished clearance. The investigation was repeated in 11 of these patients with cardiac insufficiency of Grade 3 who had improved with treatment. The clearance value was found to be only slightly altered and showed no definite pattern. It is concluded therefore that thyroid function in cardiovascular disease remains within normal limits. *S. W. Waydenfeld*

97. **Clinical Manifestations of Primary Tumours of the Left Atrium.** (К клинике первичной опухоли левого предсердия)
A. A. Šelagurov and P. N. Jurenev. *Клиническая Медицина* [*Klin. Med. (Mosk.)*] **37**, 116–123, June, 1959. 5 figs., 7 refs.

The advent of cardiac surgery has increased the importance of early diagnosis of tumours of the left atrium. These tumours are at first asymptomatic, but subsequently produce a picture similar to that of mitral stenosis. The salient diagnostic features are: (1) absence of a history of recurrent rheumatic episodes, (2) the great intensity of orthopnoea and the patient's tendency to assume unnatural positions, (3) the lack of response to the usual treatment, (4) recurrent attacks of unconsciousness, (5) variation of the murmurs with variation in the position of the patient, (6) a filling defect apparent on angiography of the left atrium (which together with the absence of a long cardiac history distinguishes a tumour from a ball thrombus of the left atrium), and (7) radiological evidence of enlargement of the left atrium and both ventricles.

In this paper 3 cases of myxoma and one of fibrosarcoma of the left atrium are described in detail. In one of these cases the tumour produced the signs of mitral stenosis and electrocardiographic evidence of infarction which results from its compression of the coronary vessels. In a second case the diagnosis was made still more difficult by a history of recurrent attacks of polyarthritis and the evidence of an active rheumatic process, while at the same time the presence of excessive orthopnoea and other signs were suggestive of a ball thrombus in the left atrium. Similarly in the third case the association of rheumatic mitral disease with a myxoma of the left atrium made the diagnosis of the latter during life impossible. Only in the fourth case was the clinical diagnosis made tentatively during life. In spite of the presence of associated mitral stenosis a correct diagnosis was made, based on the clinical and radiological findings, and was confirmed at necropsy. *S. W. Waydenfeld*

CONGENITAL HEART DISEASE

98. **The Pulmonary Arterial Reserve in Congenital Heart Disease with Pulmonary Arterial Hypertension. I. Haemodynamic Study.** (La réserve artérielle pulmonaire dans les cardiopathies congénitales avec hypertension artérielle pulmonaire. I. Étude hémodynamique)
E. Voridis, L. Scebat, J. Renais, and J. Lenègre. *Archives des maladies du cœur et des vaisseaux* [*Arch. Mal. Cœur*] **52**, 639–655, June, 1959. 6 figs., 9 refs.

When pulmonary arterial hypertension is due to increased pulmonary vascular resistance this resistance may result from fixed anatomical changes in the vessel walls, such as thickening of the intima and thrombus deposits, or from reversible spasm of the media. It is the latter factor which might be removed by surgical correction of the causative lesion in cases of congenital heart disease. For this reason the authors speak of the degree of pulmonary arterial spasm and the possibility of relieving it to allow of dilatation as the "pulmonary arterial reserve", and they have attempted to assess such reserve by measuring the pharmacodynamic response to hexamethonium or pentacynium.

In 7 patients with a left-to-right cardiac shunt and moderate pulmonary hypertension who had been fully investigated by cardiac catheterization the changes immediately following the injection of one of these drugs into the catheter were noted, oxygen being inhaled also as the drug was given. The result was an increase in pulmonary blood flow and a decrease in pulmonary pressure, the pulmonary resistance falling by an average of 50%. At the same time the systemic arterial resistance was found to fall, but to only half this extent. It is concluded that these patients had a large arterial reserve. In contrast, 3 patients with pulmonary hypertension resulting from "essential" or thrombotic causes had no arterial reserve; in these cases the pulmonary pressure and resistance did in fact fall in response to the drug, but the fall was no greater than that in the systemic circulation. A third group of 16 patients with

a considerable degree of pulmonary hypertension were similarly investigated; 5 were found to have a high reserve and 11 (including 3 cases of Eisenmenger's complex) a low reserve. Surgery was attempted in some of these cases and was successful in those in which the pulmonary arterial reserve had been high, including 2 cases of patent ductus arteriosus with gross pulmonary hypertension. *J. A. Cosh*

99. **The Pulmonary Arterial Reserve in Congenital Heart Disease with Pulmonary Arterial Hypertension. II. Functional Angiocardiographic Study.** (La réserve artérielle pulmonaire dans les cardiopathies congénitales avec hypertension artérielle pulmonaire. II. Étude angiocardiographique fonctionnelle)
L. SCEBAT, J. J. FERRANE, and J. LENÈGRE. *Archives des maladies du cœur et des vaisseaux* [*Arch. Mal. Cœur*] **52**, 656–667, June, 1959. 10 figs., 7 refs.

In this further study [see Abstract 98] the authors report angiocardiographic evidence of pulmonary vasodilatation in response to ganglion-blocking drugs in certain patients with pulmonary hypertension. Selective angiocardiography was performed with the catheter tip in the right pulmonary artery or one of its branches. Exposures at the rate of four frames per second over 5 seconds were made both before and immediately after injection of hexamethonium or pentacynium while the patient was breathing oxygen.

In 2 out of 5 patients studied there was visible dilatation of the larger pulmonary arteries, better filling of smaller branches, and a quicker flow of contrast medium through the lung. Both these patients, one a girl of 11 years with a patent ductus arteriosus and the other a girl of 17 with atrial septal defect, had pulmonary hypertension and had been shown to respond to ganglion-blocking drugs as described above, that is, they had a good " pulmonary arterial reserve ". A third similar patient, however, showed no visible vasodilatation on angiocardiography, but it was thought that this might have been due to faulty technique. In the remaining 2 patients, in whom there had been no specific pulmonary vasodilatation in the initial test, none was found in the angiocardiographic test.

Although only a few patients have as yet been studied in this way, the authors believe that it is possible to show both physiologically and radiographically whether pulmonary hypertension is reversible (that is, when it is due to arterial spasm) or not (when due to obstructive vascular changes). They also consider that when both factors contribute to the pulmonary hypertension it may be possible in this way to estimate the relative importance of each. *J. A. Cosh*

100. **Differential Lung Function in Atrial Septal Defect**
H. A. FLEMING. *Circulation* [*Circulation*] **19**, 856–862, June, 1959. 5 figs., 22 refs.

Having observed radiologically that in cases of atrial septal defect the vascular markings are more obvious in the right lung than in the left, the author, at the Brompton Hospital, London, studied by differential bronchospirometry the function of the separate lungs in 25 cases of this defect. Although the ventilatory and vital capacities of the right lung were relatively reduced, the oxygen uptake of the right lung was demonstrated by spirometry to be appreciably increased to an average of 65%, compared with a normal of 55%, and at operation the bulk of the right lung was found to be markedly increased.

There is as yet no satisfactory explanation for these findings, but it appears possible that the right pulmonary veins drain more efficiently than the left. The disparity has not been noted in reported functional studies in cases of patent ductus arteriosus or ventricular septal defect. *J. Robertson Sinton*

101. **Recatheterization of the Right Heart in Ventricular Septal Defect**
D. F. DOWNING. *American Heart Journal* [*Amer. Heart J.*] **57**, 669–673, May, 1959.

In an attempt to assess the rate of progression of pulmonary vascular changes in patients with ventricular septal defect 20 children attending the Hahnemann Hospital, Philadelphia, who had been found to have uncomplicated ventricular septal defects were re-investigated after 1½ to 8 years (mean 3·8 years), their ages at the time of the initial examination having averaged 3½ years (range 6 weeks to 13 years).

At the earlier examination 4 of the children had had a normal pulmonary arterial pressure and this had remained unchanged. Of the remaining 16, in whom the pressure had ranged between 35 and 100% of the systemic systolic pressure, the pulmonary arterial pressure had subsequently risen in only 3, while in the other 13 it was unchanged or lower. The clinical condition was unchanged in 10 and had improved in 10, the latter group including 4 who had initially been in cardiac failure; none of these had suffered a recurrence of failure and 2 were asymptomatic when re-investigated. Although the follow-up period was admittedly not long, it was clear that clinical deterioration had not occurred and that in the main pulmonary arterial pressure was more likely to fall than to rise in childhood. The author therefore suggests that in many cases of ventricular septal defect surgical cure need not be regarded as a matter of urgency and in suitable cases might be allowed to await the development of safer techniques, since, as the author remarks, " the present mortality of open-heart correction [of the defect] is far from negligible ". *J. A. Cosh*

102. **The Use of Amyl Nitrite in the Differentiation of Fallot's Tetralogy and Pulmonary Stenosis with Intact Ventricular Septum**
L. VOGELPOEL, V. SCHRIRE, M. NELLEN, and A. SWANEPOEL. *American Heart Journal* [*Amer. Heart J.*] **57**, 803–819, June, 1959. 7 figs., 16 refs.

In a previous paper (*Circulation*, 1955, **11**, 714) two of the authors reported their observations on the pulmonary systolic murmur in Fallot's tetralogy and severe pulmonary stenosis with intact ventricular septum. In the former condition it is loudest in mid-systole and finishes before or with the aortic second sound; in the latter condition it is loudest late in systole and continues

after the aortic second sound. In the present paper from the University of Cape Town and Groote Schuur Hospital they describe the influence of inhalation of amyl nitrite, which causes temporary fading of the murmur in Fallot's tetralogy and accentuation in pulmonary stenosis.

Amyl nitrite inhalation lowers peripheral resistance and systemic pressure. In patients with Fallot's tetralogy this facilitates ejection of blood from the right ventricle into the aorta, lowering the systemic arterial oxygen saturation and reducing pulmonary blood flow. This causes softening of the murmur and of the pulmonary element of the second sound. In pulmonary or infundibular stenosis the increase in systemic flow is followed in one minute by an increase in pulmonary flow, when the murmur becomes louder for a minute or two. (This is well shown in the reproductions of phonocardiograms.) Further, pressure recordings show that following amyl nitrite inhalation systemic arterial and right ventricular pressures fall in parallel in Fallot's tetralogy. By contrast, in pulmonary stenosis the initial fall in systemic pressure is followed by a considerable rise in right ventricular pressure. *J. A. Cosh*

CHRONIC VALVULAR DISEASE

103. **The Radiographic Appearances in the Lungs in Severe Mitral Stenosis.** (Imagen radiografica del pulmón en la estenosis mitral acentuada)
F. Galland, S. Aranda, S. Aceves, and N. Dorbecker. *Archivos del Instituto de cardiología de México* [*Arch. Inst. Cardiol. Méx.*] **29**, 145–174, March–April [received Aug.], 1959. 8 figs., 21 refs.

The authors have sought to correlate the radiographic appearances of the lungs in 20 cases of mitral stenosis before and after commissurotomy with the capillary pressures revealed by catheterization, with the size of the mitral orifice as found at operation, and also with such evidence of the severity of veno-capillary hypertension as haemoptysis, blood-stained sputum, and various grades of dyspnoea. In respect of each of these findings the cases were classified in four grades, the criteria for grading being given in detail.

In each of the cases studied mitral stenosis was either the sole or the predominant lesion and in each the mitral orifice proved to be less than 1 sq. cm. in area. There were 10 males and 10 females ranging in age from 13 to 45 years. Enlargement of the hilar shadow was present in every case, the authors' observations being made mainly on the right hilum since the left hilum is often largely masked by the heart and may be hidden by the enlarged pulmonary artery and by part of its left main branch. Vascular reticulation extended into the outer third of the lung fields and towards the apices. Fine miliary mottling, most marked in the middle third of the lung fields, was seen in 20% of cases. The B lines of Kerley—septal lymphatic lines, horizontal, 4 to 5 mm. long and 1 mm. wide, and most obvious in the region of the costophrenic sinuses—were noted in 89% of cases. Such lines never occurred as isolated findings; they would seem to be concomitant with high pulmonary capillary pressure. A linear effusion revealing the normally invisible pleural margin was present in 14 cases. This was mainly obvious immediately above the costo-phrenic sinus and was often associated with a small costo-phrenic effusion. It usually disappeared within 2 to 6 months of operation. Abnormality of the horizontal fissure was revealed by undue widening, particularly towards the hilum. Grading according to radiological appearances of the lung coincided with that based on the mitral area in 18 out of 19 cases (94·7%), with that based on the clinical signs of veno-capillary hypertension in 16 out of 20 cases (80%), and with that based on pulmonary capillary pressure readings in no more than 9 out of 14 cases (64·2%). The authors claim that despite the small number of cases in the series these findings are of some significance.

Grading based on the postoperative radiographic appearances coincided with that based on the degree of enlargement of the mitral opening which was found possible at operation in 17 out of 18 cases (94·4%). Radiological abnormalities often vanished during the first 2 months after operation, but in more severe cases the fine, diffuse mottling persisted for 6 months to 3 or 4 years. Such persistence may indicate that the miliary appearance is due to haemosiderosis.

A. C. F. Green

104. **Prognosis after Mitral Commissurotomy: Factors Affecting Results in Ninety-two Patients**
I. J. Adatto and H. A. Bliss. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **170**, 1011–1018, June 27, 1959. 20 refs.

A review is presented of the results of mitral commissurotomy in 92 patients treated during the period 1951–7 at the University of Illinois Research and Educational Hospitals, with a follow-up of one to 5 years. All the patients had maximum medical treatment before operation, and most of them (64) were in Group 3 of the functional classification of the New York Heart Association, 16 being in Group 2 and 12 in Group 4. Commissurotomy was performed either by finger fracture or incision, with an operative mortality of 8% (7 patients); 19 more patients, 12 of whom had shown initial improvement, died within 6 weeks to 6 years of operation, the cause being known to be cardiac in 11 cases. On review of the survivors at least 18 months after operation sustained improvement was found in 43 patients (47% of the whole series); 16 (17·4%) had deteriorated after initial improvement; and 7 patients (7·6%) had experienced no improvement.

The following factors were found to influence the results adversely: (*a*) poor preoperative function; (*b*) presence of atrial fibrillation before operation; (*c*) mitral insufficiency present at operation; (*d*) associated valvular lesions and hypertension; (*e*) severe calcification of the mitral valve; (*f*) preoperative cardiac enlargement; (*g*) large size of the mitral orifice before operation; and (*h*) diameter of the mitral orifice after operation less than 20 mm. The two most important factors were (*c*) and (*h*). Even mild mitral incompetence influenced prognosis adversely.

It was disappointing that late deterioration followed initial improvement in several cases despite apparently adequate commissurotomy and absence of other adverse prognostic factors. The authors postulate that gradual re-stenosis, myocardial insufficiency, or both may cause late failures. The prognosis for patients in any given functional group after operation without any of the above-mentioned adverse factors was less good than might be predicted for medically treated patients in the same functional class, while deterioration after operation, when it occurred, was more rapid than in patients treated medically.

The authors conclude that operation should be advised in cases of mitral stenosis when there is: (1) absence of a high-pitched apical systolic murmur louder than Grade 2 in intensity; (2) minimal calcification of the mitral valve or none; (3) absence of electrocardiographic evidence of left-sided hypertrophy or of mitral insufficiency; (4) a cardio-thoracic ratio of less than 61%. Of the 37 patients in their series who satisfied all these criteria, 2 died at operation, 34 (92%) improved initially, and 28 (76%) maintained their improvement. Of the 38 patients who failed to meet one or more of these criteria, improvement was sustained in only 9 (24%).

C. A. Jackson

105. **The Postmitral Commissurotomy Syndrome: a Four-year Clinical, Pathologic and Serologic Study, and Its Relation to Restenosis**

P. LISAN, A. REALE, and W. LIKOFF. *Annals of Internal Medicine* [*Ann. intern. Med.*] **50**, 1352–1358, June, 1959. 3 figs., 9 refs.

From the Hahnemann Medical College and Hospital and the Bailey Thoracic Clinic, Philadelphia, a study is reported of the post-mitral-valvotomy syndrome in 78 patients (47 female and 31 male) aged 30 to 50 years observed for periods ranging from 3 months to over 4 years. Also included in the study were 5 males operated on for coronary arterial disease and 10 for congenital heart disease and observed for a similar period. Before operation the history and results of a physical examination were studied for evidence of rheumatic activity and a number of laboratory investigations were carried out, including a complete blood count and estimation of the erythrocyte sedimentation rate (E.S.R.) and of antistreptolysin and antihyaluronidase titres. Biopsy specimens of the left atrial appendage were obtained at the time of operation.

The syndrome developed in 21 patients (18 female and 3 male), the first attack occurring within one month of operation in 7 cases and as late as 10 months afterwards in 4; in 17 the syndrome developed within 4 months. Multiple attacks occurred in 13 cases, with intervals between attacks of 1 to 4 months in 6 and more than 4 months in the remaining 7. The duration of the attacks varied and did not follow any specific pattern.

Clinically, the most constant manifestations were recurrent low-grade fever and thoracic pain, usually of a pleuritic or pleuro-pericardial nature. A pericardial friction rub was the characteristic physical finding, but no pleural friction rubs were heard. Right heart failure did not occur and no new murmurs were elicited; there were no significant changes, clinically or radiologically, in the size of the heart. The E.S.R. was raised in 2 cases, and the antistreptolysin and antihyaluronidase titres rose significantly in one patient only. In the remaining 57 patients who did not develop this syndrome the results of the laboratory studies were normal before and after operation. The atrial biopsy specimens showed no evidence of recurrent or acute rheumatic carditis.

Treatment consisted in administration of salicylates, cortisone, hydrocortisone, and antibiotics; no advantage was to be gained by giving steroids in preference to salicylates as regards duration, severity, or complications of the post-commissurotomy syndrome.

The syndrome was not observed in any of the patients with coronary arterial disease or in the 10 with congenital heart disease. Re-stenosis of the mitral valve did not develop during a 4-year follow-up period in any of the patients with the post-commissurotomy syndrome.

According to the authors the syndrome is a clinical entity readily distinguishable from the active rheumatic state, but the aetiology remains obscure.

A. J. Karlish

CORONARY DISEASE AND MYOCARDIAL INFARCTION

106. **Plasma Catechol Amine Concentrations in Myocardial Infarction and Angina Pectoris**

P. C. GAZES, J. A. RICHARDSON, and E. F. WOODS. *Circulation* [*Circulation*] **19**, 657–661, May, 1959. 1 fig., 20 refs.

A study of the plasma catechol amine levels in patients with acute myocardial infarction or angina pectoris in comparison with those in patients with pain of non-cardiac origin and normal subjects is reported from the Medical College of South Carolina, Charleston. In all of 13 patients with myocardial infarction the plasma noradrenaline level within the first 36 hours of the attack was significantly higher than the mean value for 7 control subjects, and in 7 of the patients the plasma adrenaline level was also above the normal range. In 11 cases in which the estimations were repeated 72 hours after the attack the noradrenaline level had fallen to within the normal range. There was a significant correlation between the plasma noradrenaline level and the serum transaminase activity. In 6 patients with non-cardiac pain the plasma catechol amine levels were within the normal range. Of 12 patients with angina pectoris, the plasma noradrenaline level increased with exercise in 8 and that of adrenaline in 5, whereas in the 6 normal subjects there was no significant change with exercise. It is suggested that the increased plasma concentrations of noradrenaline and adrenaline after myocardial infarction and in patients with angina pectoris after exercise may be due to the liberation of these amines not only from the adrenal medulla, but also from the myocardium, anoxia and the accumulation of lactic acid causing their release from the chromaffin tissue within the heart. Such a release might not only intensify the pain, but also act as a local factor exciting ventricular arrhythmias.

C. Bruce Perry

107. **Intravenous Injection of Hyaluronidase in Acute Myocardial Infarction: Preliminary Report of Clinical and Experimental Observations**
J. MARTINS DE OLIVEIRA, R. CARBALLO, and H. A. ZIMMERMAN. *American Heart Journal* [*Amer. Heart J.*] **57**, 712–722, May, 1959. 13 figs., 15 refs.

This report from St. Vincent Charity Hospital, Cleveland, Ohio, describes a trial of the intravenous infusion of hyaluronidase—given in the belief that it may limit the development of oedema in the myocardium immediately after infarction—which was carried out on 6 patients with unequivocal evidence of the occurrence of infarction not more than 8 hours previously. As well as morphine, oxygen, anticoagulants, and bed rest, these patients were given an infusion of a special preparation of hyaluronidase in a dose of 100,000 units 6-hourly for the first day, 8-hourly for the next 2 days, and 12-hourly for a further 2 days. All made an uncomplicated recovery and began to show electrocardiographic improvement after the first dose. Depressions and elevations of the S–T segment were largely corrected, and in one case total heart block reverted to normal conduction in 8 hours, while in another right bundle-branch block showed improved conduction in 2 hours; Q waves were unchanged.

In further experimental studies ligation of an anterior branch of the left coronary artery was performed in 7 dogs, after which serial electrocardiograms (ECG) were recorded from epicardial leads while an infusion of 100,000 units of hyaluronidase was given. Striking changes in the ECG were seen within a few minutes, with diminution of the " current of injury " and reversion of the tracing towards normal. The precise mode of action of hyaluronidase is not known, but it clearly appears to lessen the immediate damage to the myocardium.

J. A. Cosh

108. **Action of Nitroglycerin on the Coronary Circulation in Normal and in Mild Cardiac Subjects**
N. BRACHFELD, J. BOZER, and R. GORLIN. *Circulation* [*Circulation*] **19**, 697–704, May, 1959. 27 refs.

By means of cardiac catheterization and catheterization of the coronary sinus the effect on the coronary blood flow of sublingual administration of 0·6 mg. of nitroglycerin was studied in 4 normal subjects and 6 with signs of mild cardiac disorder (mostly functional murmurs) at the Peter Bent Brigham Hospital (Harvard Medical School), Boston, and the U.S. Naval Hospital, Portsmouth, Virginia. After the administration of nitroglycerin myocardial oxygen consumption and coronary blood flow increased and coronary vascular resistance fell, but cardiac work was unchanged and cardiac efficiency fell. Cardiac output showed little change and there was a slight fall in peripheral blood pressure. The pulmonary arterial, pulmonary wedge, and right auricular pressures fell considerably.

It has been shown *in vitro* that various nitrites increase the oxygen consumption of muscle by the uncoupling of oxidative phosphorylation, and it is suggested that this may account for the increase in myocardial metabolism with no increase in cardiac work observed in these experiments.

C. Bruce Perry

109. **Effect of Nitroglycerin on the Coronary Circulation in Patients with Coronary Artery Disease or Increased Left Ventricular Work**
R. GORLIN, N. BRACHFELD, C. MACLEOD, and P. BOPP. *Circulation* [*Circulation*] **19**, 705–718, May, 1959. 40 refs.

The haemodynamics of the coronary, pulmonary, and systemic circulations and the metabolism of the heart were studied by the methods previously used [see Abstract 108] before and after the sublingual administration of 0·6 mg. of nitroglycerin in 7 patients with coronary sclerosis and angina pectoris and 10 with increased left ventricular work—due in 3 cases to mitral insufficiency, in 4 to aortic stenosis, and in 3 to aortic insufficiency—7 of the 10 also having angina pectoris. The administration of nitroglycerin resulted in a decrease in cardiac output, blood pressure, and left ventricular work in both groups and caused a fall in systemic and pulmonary venous pressures. Coronary blood flow and myocardial oxygen consumption were unchanged or actually fell, there was no change in coronary vascular resistance, and cardiac efficiency was reduced.

It is argued that the vasodilator capacity of the heart was already exhausted in these subjects either as a result of coronary arterial disease or overloading of the left ventricle. It is suggested that difference in the reaction to nitroglycerin between the normal and the diseased coronary circulation might afford a method of assessing the efficiency of the coronary circulation. It is difficult to explain the relief of pain in angina pectoris by nitroglycerin on the basis of present theories of its action if these results are confirmed. It may be that nitroglycerin achieves its striking effect in angina pectoris by decreasing the contractility of the heart rather than by increasing coronary blood flow.

C. Bruce Perry

110. **Statistical Associations between International Coronary Heart Disease Death Rates and Certain Environmental Factors**
N. JOLLIFFE and M. ARCHER. *Journal of Chronic Diseases* [*J. chron. Dis.*] **9**, 636–652, June, 1959. 2 figs., 32 refs.

This paper from the Department of Health of the City of New York is a contribution to the controversial issue of the relation of diet to coronary heart disease. The results of correlating the *quantity* of intake of fat in different countries with their death rates from coronary disease have been inconsistent, but there is some evidence of an association between the ratio of hard fats to oils consumed and mortality from coronary disease—that is, that the *quality* of fat consumed is of greater importance than the quantity. This evidence, however, is based on data from only a few countries, and the present authors attempt to repair this deficiency by examining statistics provided by the World Health Organization and dietary information provided by the Food and Agriculture Organization of the United Nations for 20 different countries.

The death rates for men in the age group 55–59 from arteriosclerotic and degenerative heart disease for these countries (ranging from 68 to 704 per 100,000) were

correlated with the total fat intake and the intake of saturated and unsaturated fat and of animal protein, all expressed as percentages of the average total caloric intake per head.

The highest degree of association with the death rate from arteriosclerotic and degenerative heart disease was given by the data for saturated fat intake (r=0·83), but almost as close a relationship was found with both animal protein intake (r=0·80) and total fat intake (r=0·73). Furthermore, while the factor of saturated fat intake could be shown to account for 68% of the variation in the death rates of these 20 countries, those of animal protein intake and total fat intake accounted for 64% and 54% respectively of that variation. Such overlapping could arise only from the intercorrelation of these variables, which suggested that the statistical association between coronary mortality and saturated fat intake might be enhanced by considering two dietary factors at a time. In the event, although multiple correlation procedures indicated that the combination of any of these factors with saturated fat intake accounted for but little more of the death rate variation, they demonstrated that the intake of saturated fats was 1·6 times more important than that of animal protein, 7 times more important than the daily calorie intake, 25 times more important than the total fat intake, and 51 times more important than the unsaturated fat intake in accounting for the variations. For 14 of the 20 countries the death rates of males in the same age group (55–59) for arteriosclerotic heart disease *per se* (that is, excluding deaths, irrelevant in this context, classified as due to chronic endocarditis or to other myocardial degeneration) were available. When this refined classification was used the correlation with saturated fat intake was enhanced (r=0·91), and this dietary factor was found to account for 83% of the death rate variation.

The authors also examined the association between three indices of environment and mortality from arteriosclerotic and degenerative heart disease in all 20 countries. They found that the mortality from heart disease rose with the economic level of the country as indicated by the average daily caloric intake per head (r=0·55). The general death rate of males in the age group 55–59, used as an indication of the over-all health of the country and possibly as a reflection of its level of medical sophistication, was negatively correlated with mortality from heart disease (r=−0·28). The finding that the number of telephones per 100 of the population—as a measure of stress and strain such as is generally ascribed to Western civilization—was positively correlated with mortality from heart disease (r=0·69) and with saturated fat intake (r=0·75) leads them to make the interesting speculation that " many of the effects of stress and strain . . . result from an increased consumption of saturated fats ".

It is the authors' view that this demonstration that the intake of saturated fat is an important factor in determining the differences between the death rates from heart disease in 20 countries and that the other dietary factors examined gave little aid to the saturated-fat intake in accounting for the differences supports the theory that " indicts the intake of saturated fats as one of the principal epidemiologic associations with coronary heart disease and is a possible explanation why certain countries . . . with high total fat intakes also exhibit relatively low coronary heart disease death rates ".

E. Lewis-Faning

111. **The Effects of Vitamin B_1 on the Coronary Circulation and on Carbohydrate Metabolism.** (Влияние витамина B_1 на коронарное кровообращение и углеводный обмен)

B. A. Ovčinnikov. *Клиническая Медицина* [*Klin. Med.* (*Mosk.*)] **37**, 123–130, June, 1959. 13 refs.

The author describes a clinical trial of vitamin B_1 (aneurine) in 131 patients, of whom 33 were suffering from angina, 41 from myocardial infarction, 36 from hypertensive disease without precordial pain, and 21 from valvular disease and atherosclerosis with Grade-3 heart failure; 12 healthy subjects served as controls. Investigations before and after treatment included recording of the electrocardiogram (ECG) and estimations of the pyruvic acid level in the blood and urine and the urinary excretion of vitamin B_1. The vitamin was administered intravenously in doses of 30 mg. daily for 10 to 15 days.

The anginal pain disappeared in 15, diminished in 14, and became less frequent, though of unaltered intensity, in 2 of the 33 patients with angina. Of the 41 patients with myocardial infarction, pain disappeared in 22, diminished in 15, and remained the same in 4, while the ECG became normal in a small proportion of patients. The systolic blood pressure increased in 10, diminished in 31, and was not altered in 69 of the 110 patients with angina or myocardial infarction combined with hypertension, while the diastolic pressure was diminished in 21, increased in 6, and remained unchanged in 83 patients. Any increase in blood pressure was temporary and followed only the first course of injections of the vitamin.

The blood pyruvic acid level in patients with angina was usually normal. A slight increase in this level was observed in 12 of the patients with atherosclerosis, but it returned to normal after treatment with the vitamin. A greater increase in pyruvic acid level was observed in 27 out of 40 patients with myocardial infarction, but the level returned to normal in 16 cases after one or two courses of vitamin B_1. A slightly smaller increase took place in 25 of 36 patients with hypertensive disease, in 14 of whom it diminished after vitamin therapy. Of 21 cases of valvular disease or atherosclerosis, the blood pyruvic acid level was increased in 17 and returned to normal after treatment in only 2 cases. Increased pyruvic acid concentration in urine was more common than in the blood and was thus an earlier indication of the disturbance of carbohydrate metabolism. This concentration also usually diminished after the course of the vitamin. Abnormal blood sugar curves became normal in a high proportion of patients in all groups except those with Grade-3 heart failure. The concentration of vitamin B_1 in 24-hour specimens of urine was diminished in all patients with increased blood pyruvic acid levels.

It is suggested that disorders of carbohydrate metabolism produced by a variety of exogenous and endogenous factors similar to those influencing the regulatory

mechanism of the blood pressure and coronary circulation seem to play a part in the pathogenesis of these cardiovascular diseases, and that the administration of vitamin B_1, by correcting the reflex regulation of carbohydrate metabolism and by increasing the coronary flow, improves the nutrition of the myocardium.

S. W. Waydenfeld

DISTURBANCES OF RHYTHM AND CONDUCTION

112. **Vasopressor Therapy in the Cardiac Arrhythmias**
H. GOLD and E. CORDAY. *New England Journal of Medicine* [*New Engl. J. Med.*] **260**, 1151–1156, June 4, 1959. 8 figs., 27 refs.

In this paper from the University of California School of Medicine and the Cedars of Lebanon Hospital, Los Angeles, the authors describe their method of terminating paroxysms of supraventricular and ventricular tachycardia, atrial fibrillation, complete atrioventricular heart block, Wenckebach's phenomenon, sinus bradycardia, and frequent ventricular extrasystoles by administration of vasopressor drugs and report 6 cases in detail. In some patients the drug did not terminate the attack, but did sustain blood pressure and coronary flow until other anti-arrhythmic agents took effect. Since excessive hypertension may induce further ventricular tachycardia, the authors recommend administration of the short-acting drug noradrenaline by slow intravenous drip. They state that it is important to treat patients with coronary arterial disease as soon as such arrhythmia occurs, since myocardial necrosis may result, particularly if hypotension exists. When vagal stimulation fails in such patients vasopressor therapy should be instituted and continued, even if it is unsuccessful in aborting the arrhythmia, while procainamide, quinidine, or digitalis are being administered as anti-arrhythmic drugs.

The authors consider that this regimen will reduce the high mortality which accompanies cardiac arrhythmia following myocardial infarction. *T. Semple*

113. **Functional Angina Pectoris Due to Atrio-ventricular Block.** (L'angine de poitrine fonctionnelle du bloc A–V)
R. FROMENT, D. DE GEVIGNEY, A. PERRIN, and J. NORMAND. *Archives des maladies du cœur et des vaisseaux* [*Arch. Mal. Cœur*] **52**, 481–489, May, 1959. 5 refs.

An account is given of 3 patients in whom the onset of bradycardia due to atrio-ventricular (A–V) block was clinically associated with typical angina pectoris. In all 3 cases subsequent post-mortem examination showed that the main coronary trunks were unobstructed, while in one case there was no evidence at all of coronary arterial disease.

On the basis of these findings the authors suggest that bradycardia itself can be responsible for functional coronary insufficiency, at least in the presence of other contributory factors—all 3 patients were moderately hypertensive and one also had aortic incompetence—and that the mechanism of production of the angina is probably through the reduction in coronary arterial blood flow which results from the abrupt fall in cardiac output following A–V block. Thus it has been shown in dogs that both cardiac output and coronary blood flow decrease by about 50% immediately after experimental induction of A–V block, but that some 24 to 48 hours later this decrease is followed by a gradual return of these values to between 70 and 80% of control levels. The latter observation is in accord with the clinical course in 2 of the patients described, in whom the angina subsequently diminished despite persistence of the bradycardia and reduced cardiac output. *S. G. Owen*

HEART FAILURE

114. **Body Fluid Alterations during the Development of and Recovery from Hyponatremia in Heart Failure**
J. R. JAENIKE and C. WATERHOUSE. *American Journal of Medicine* [*Amer. J. Med.*] **26**, 862–868, June, 1959. 1 fig., 25 refs.

The authors report from the University of Rochester School of Medicine, New York, the results of balance studies carried out on 4 patients with advanced heart failure and hyponatraemia. Observations were made in one case during the development of hyponatraemia, and in all 4 during correction of the sodium balance.

During development of hyponatraemia the retention of water and the small external sodium loss accounted for only a small part of the fall in the serum sodium concentration. The authors consider that alteration in internal electrolyte distribution is largely responsible, pointing out that further evidence for this mechanism is provided by the fact that most patients in heart failure can tolerate large water loads. In patients with hyponatraemia accompanied by cardiac failure and oedema loss of electrolytes in excess of water following administration of mercurial diuretics was not observed. It is unlikely, therefore, that diuretics play much part in producing this electrolyte disturbance.

During recovery from hyponatraemia there was either a loss of body water associated with a positive cation balance or a loss of water which was hypotonic relative to the cation concentration in the serum. A rise in serum sodium concentration therefore resulted. Sodium retention is not necessary for the correction of hyponatraemia. *David Phear*

115. **Clinical Observations on the Oral Diuretic Methforylthiazidine (Rontyl)**
T. B. COUNIHAN and I. FARRELL. *Journal of the Irish Medical Association* [*J. Irish med. Ass.*] **44**, 130–134, May, 1959. 5 figs., 7 refs.

Diuresis dependent on the inhibition of carbonic anhydrase activity in the renal tubule cells can be effected by certain benzene disulphonamide compounds, the activity of which is influenced by substituents in the benzene ring. Methforylthiazidine (" rontyl ") differs from chlorothiazide by the replacement of a saturated ring for the unsaturated thiadiazine ring and the substitution of a trifluoromethyl group in place of chlorine. Rontyl was administered to 50 patients in congestive cardiac failure

at the Mater Misericordiae Hospital, Dublin. Ward patients were on low-salt diet, while out-patients took a liberal diet without added salt. Cases are described to illustrate the acute diuretic response. There was a marked increase in the rate of excretion and total excretion of sodium and chloride ions in 24 hours; the total potassium excretion was slight. Bicarbonate loss due to carbonic anhydrase inhibition was increased, the peak at 2 hours being slightly in advance of peak electrolyte excretion. Optimum dosage was found to lie between 50 and 100 mg. " morning and midday "; experimental increase of dosage failed to enhance, and sometimes diminished, the response. Diuresis began one hour after administration, reached a peak at 3 to 3½ hours, and diminished after 4 hours. Repeated treatment (illustrated by one case history) produced on every occasion adequate diuresis, increased sodium and chloride excretion, and loss of weight, but no side-effects or evidence of renal damage.

It is advocated that, although the kaliuretic effect of rontyl is slight, potassium should be administered in long-term treatment because the cumulative effect can be significant, especially if digitalis is given concurrently. In comparative studies 125 mg. of rontyl by mouth was equivalent in potency to 2,000 mg. of chlorothiazide orally or 2 ml. of mersalyl intramuscularly. *R. S. Stevens*

SYSTEMIC CIRCULATORY DISORDERS

116. Effect of Age and Coronary Artery Disease on the Postural Adjustment of Peripheral Circulation

E. SIMONSON. *Circulation Research* [*Circulat. Res.*] **7**, 442–447, May, 1959. 2 figs., 11 refs.

In order to confirm that changes in posture have more effect upon the circulation of the aged than in the young because in the former compensatory reflexes are less efficient, the author, working at the University of Minnesota, compared the pulse amplitude in 26 men of mean age 58 with that in 26 men of mean age 25 while the patients were first tilted 45 degrees head-up for 5 minutes, and then 15 degrees head-down for 2 minutes. The pulse was recorded by an impedance plethysmograph, the principle of which is described, from electrodes on the forehead and occiput. In both directions of tilt the change of pulse amplitude was greater in the older men. During the period of tilting up the pulse recovered its normal amplitude within 5 minutes in the younger group only. In all subjects the fall in pulse amplitude on tilting up was less than the rise on tilting down, showing that there is more efficient compensation in the upright position.

A study was also made of 18 normotensive patients of mean age 60 suffering from coronary arterial disease. Surprisingly enough, when tilted head-up these subjects showed an increase instead of a decrease in pulse amplitude, and when tilted head-down they showed a lesser increase of amplitude than the older normal subjects of similar age. The author suggests that the carotid sinus may be hypersensitive in patients with coronary disease. *D. Goldman*

117. The Mode of Action of Chlorothiazide in Hypertension: with Special Reference to Potentiation of Ganglion-blocking Agents

C. T. DOLLERY, M. HARINGTON, and G. KAUFMANN. *Lancet* [*Lancet*] **1**, 1215–1218, June 13, 1959. 2 figs., 16 refs.

The mechanism of potentiation by chlorothiazide of the hypotensive action of ganglion-blocking drugs was studied at the Postgraduate Medical School of London. A single intravenous injection of 0·5 g. of chlorothiazide was given to 3 hypertensive patients without heart failure, but there was no resulting change in blood pressure. In 4 similar patients the response of the blood pressure to an intravenous injection of 2·5 mg. of pentolinium was found to be uninfluenced by previous intravenous administration of 0·5 to 1 g. of chlorothiazide. Of a further group of 13 patients given 1 g. of chlorothiazide twice daily by mouth for 4 days, 5 showed a slight fall in casual blood pressure readings and 2 a slight rise. Postural hypotension developed in 4 of these patients. In 9 of the 13 there was increased sensitivity to the hypotensive effect of pentolinium, and in 8 of these 9 a fall in plasma volume was observed 3 days after starting chlorothiazide. Sensitivity to pentolinium returned to the pre-chlorothiazide value in 6 of the 8 patients after the plasma volume had been restored to its control level by infusion of salt-free dextran. Other changes occurring after treatment with chlorothiazide were diuresis, loss of weight, loss of potassium, and a rise in the blood urea level. In 11 of the 13 patients a loss of sodium was noted after 3 days 'treatment with chlorothiazide, and 8 of these showed a fall in plasma volume and increased sensitivity to pentolinium; the extent of the sodium loss, however, did not correlate well with the increased sensitivity to pentolinium.

The authors do not consider that chlorothiazide has a direct hypotensive action of its own; in their view the increased sensitivity to pentolinium which develops in patients receiving chlorothiazide and which affects particularly the postural fall in blood pressure is due mainly to the fall in plasma volume and partly to sodium depletion when this is very marked.

Bernard Isaacs

118. Effects of Intravenous Hydration and Pitressin on Renal Function in Subjects with Essential Hypertension

W. HOLLANDER. *Circulation* [*Circulation*] **19**, 691–696, May, 1959. 9 refs.

The correction by hypotensive drugs of the excessive urinary excretion of sodium in essential hypertension suggests that certain disturbances of water and electrolyte metabolism in this disease may be the result rather than the cause of the high blood pressure. To test this hypothesis 5% glucose in water was infused intravenously at the rate of 14 ml. per minute into 9 normal and 11 hypertensive subjects at the Massachusetts Memorial Hospitals (Boston University School of Medicine), Boston. Although the rate of flow during a control period was comparable in the two groups, the maximum urinary flow induced by the infusion was appreciably less in the hypertensive than in the control group. After periods

of treatment with various hypotensive drugs, however, the response of the hypertensive subjects was significantly increased. The renal response to "pitressin" (vasopressin) was comparable in the two groups. The increased sodium excretion reported by Ek to occur in hypertensive subjects during the infusion of glucose was not observed. *J. McMichael*

119. **Water and Salt Excretion after Intravenous Salt Load in Hypertensive Subjects**
T. D. ULLMANN, S. H. BLONDHEIM, S. DIKSTEIN, and D. BEN-ISHAY. *Circulation* [*Circulation*] **19**, 729–734, May, 1959. 2 figs., 22 refs.

In 20 hypertensive and 31 normal control subjects studied at the Rothschild–Hadassah University Hospital, Jerusalem, the excretion of water and salt after an intravenous load of 5% saline (100 ml. per sq. m. body surface in 30 minutes) was determined. During the diuresis which followed the infusion the hypertensive subjects excreted both water and salt at higher rates than the normal subjects, the diuretic response of the former being greater than the saluretic response. At low rates of urinary flow, however, the salt excretion of the hypertensive subjects was less than that of the controls. This last finding is compatible with the hypothesis of the existence of a "salt-retaining" mechanism in the hypertensive state, and it is suggested that the more rapid excretion of salt at high rates of urine flow may result from the sweeping of salt through the proximal tubule faster than the distal tubule can handle it.

J. McMichael

PERIPHERAL ARTERIES

120. **Enzyme Treatment of Arteriosclerosis Obliterans.** (Enzymterapi ved arteriosclerosis obliterans)
O. SELVAAG, H. KJØRSTAD, and L. HILLESTAD. *Nordisk Medicin* [*Nord. Med.*] **61**, 713–717, May 7, 1959. 2 figs., 11 refs.

Following reports that a new enzyme preparation, "vasolastine", which consists of a mixture of 30 mg. of citrogenase–lipoxydase, 20 mg. of amino-acid oxydase, and 20 mg. of tyrosinase–tryptase, has proved effective in causing the disappearance of atheromatous deposits, the authors carried out a clinical trial on 26 cases of peripheral or coronary atheroma at the Ullevål Hospital, Oslo. As the preparation had not been stored under optimum conditions when the first 6 patients were treated, only the last 20 patients, 18 men and 2 women aged between 46 and 74 years, are considered here. Of these patients, 17 were suffering from peripheral arterial disease and 3 from coronary atheroma, the latter all having suffered myocardial infarction. Vasolastine was administered intramuscularly in a dose of 2 ml. three times weekly; treatment was continued for periods ranging from 2 to 14 months, 11 of the patients being treated for more than 6 months and 3 for more than one year.

Subjective improvement was noted by 5 patients with intermittent claudication and by one with angina, in 2 cases the "claudication distance" increasing from approximately 50 metres to 1·2 and 5 km. respectively. Arteriographic studies, however, showed further progressive changes in the femoral arteries in all cases, and it is assumed that improvement was brought about mainly by changes in the collateral circulation. Contrary to previous claims, the authors did not notice any significant changes in the serum cholesterol level either during or after treatment. No changes in skin or muscle temperature were noted after injecting vasolastine.

H. F. Reichenfeld

121. **Investigation of Thyroid Function in Patients with Atherosclerosis.** (Исоледование функции щитовидной железы у больных атеросклерозом)
A. N. MITROPOLBSKIJ and A. F. MURČAKOVA. *Клиническая Медицина* [*Klin. Med.* (*Mosk.*)] **37**, 89–92, June, 1959. 1 fig., 16 refs.

The role of hypothyroidism in the development of hypocholesterolaemia is well known. At the University and Academy of Military Medicine, Leningrad, thyroid function was studied by means of the radioactive iodine uptake test in 48 patients (30 males and 18 females aged 39 to 88 years) with the predominantly cardiac form of atherosclerosis and in 10 healthy individuals who served as controls. The dose of ^{131}I was 1 to 2 μc. and the results were expressed as the percentage of the dose removed by the thyroid gland 2, 4, 8, 24, 48, and 72 hours after its oral administration.

In 13 (27%) of the patients uptake of ^{131}I was grossly diminished (1·5% at 2 hours and 0·8 to 14% at 24 hours), and it was at the lower limit of normal in the remainder. In another group of 16 patients with cardiovascular disease but no evidence of atherosclerosis the uptake values were normal. It seems therefore that circulatory failure *per se* does not reduce the uptake of ^{131}I by the thyroid gland. No correlation was observed between the results of the uptake test on the one hand and changes in the electrocardiogram, weight, and basal metabolic rate (B.M.R.) on the other. The B.M.R. was considerably diminished in 16 of the 20 patients in whom it was determined, but it seemed to reflect a different aspect of thyroid function and therefore could be affected by atherosclerosis in a different way. Low values for uptake of ^{131}I were more common in (1) patients with more widespread atherosclerosis (especially if there was involvement of the cerebral vessels in addition to that of the coronary arteries), (2) those with a longer history of the condition and a higher blood cholesterol concentration, and (3) patients in the higher age groups.

The authors suggest that the diminished uptake of ^{131}I in these cases may be connected with the changes in the vascular supply to the thyroid gland itself.

S. W. Waydenfeld

122. **Function Test for Peripheral Arterial Circulatory Insufficiency in the Lower Extremities in Obstructive Arterial Disease.** [Monograph, in English]
B. L. LINDSTRÖM. *Acta chirurgica Scandinavica* [*Acta chir. scand.*] Suppl. 242, 1–128, 1959. 23 figs., bibliography.

Clinical Haematology

123. **Pyridoxine Deficiency in Haematological Diseases.** (Vitamin-B_6-Mangelzustände bei hämatologischen Krankheiten)
G. GEHRMANN. *Deutsche medizinische Wochenschrift* [*Dtsch. med. Wschr.*] **84**, 1165–1168, June 26, 1959. 1 fig., 35 refs.

Less then 50 mg. of xanthurenic acid is excreted by the normal subject in the 24 hours following an oral dose of 10 g. of DL-tryptophan, but when pyridoxine (vitamin-B_6) deficiency exists this level is exceeded and excretion may reach 120 mg. a day. The tryptophan tolerance test was carried out on 159 patients with various haematological disorders and gave a positive result in 23 cases. In general, normal results were obtained in iron-deficiency anaemia, lymphatic leukaemia, hepatic cirrhosis with or without anaemia, nephrogenous anaemia, aplastic anaemia, and pernicious anaemia. The result was positive in 9 out of 12 cases of anaemia associated with a tumour, but in only one out of 17 cases of tumour without anaemia. The remaining positive results occurred in cases of acute leukaemia (2 out of 4), iron-deficiency anaemia (one out of 16), chronic myeloid leukaemia (2 out of 6), monocytic leukaemia (one), lymphosarcoma (2 out of 3), γ myeloma (2 out of 3), disseminated lupus erythematosus (one), hepatogenous anaemia (one out of 5), and achrestic anaemia (one out of 4). *M. Lubran*

124. **The Alcohol-intolerance Syndrome in Hodgkin's Disease.** [In English]
J. BICHEL. *Acta medica Scandinavica* [*Acta med. scand.*] **164**, 105–112, 1959. 26 refs.

In 1950 Hoster observed that some patients with Hodgkin's disease experience pain following the ingestion of even small amounts of alcohol. Of 166 patients with Hodgkin's disease seen at the Cancer Clinic and Institute of General Pathology, University of Aarhus, Denmark, since 1950, 25 showed intolerance to alcohol when given lager beer containing 10 g. of ethyl alcohol. Though intense and often radiating pain in one or more of the sites involved by the lymphogranulomatous process was the most frequent symptom, it was rarely the only symptom and in some cases did not occur at all. Other signs and symptoms in order of frequency were malaise, paraesthesiae which often superseded the pain, paresis, anxiety, oppression, dyspnoea, sensation of suffocation, severe itching, dizziness and flickering before the eyes, palpitations, nausea, coughing, and chills. Symptoms developed within a few minutes of taking the alcohol, and during the attack, which lasted from 30 minutes to 2 hours, some patients looked critically ill and greatly depressed. Many patients had been unaware of this intolerance. In some it developed only after an exacerbation of the disease and disappeared again after a course of radiotherapy or chemotherapy.

The author states that alcohol intolerance in patients suffering from diseases other than Hodgkin's disease is so rare that its occurrence is of some diagnostic value in the latter disease. Various hypotheses concerning the mechanism of the alcohol intolerance syndrome are discussed. *A. Ackroyd*

125. **Auto-immunity in Man and Homologous Disease in Mice in Relation to the Malignant Lymphomas**
H. S. KAPLAN and D. W. SMITHERS. *Lancet* [*Lancet*] **2**, 1–4, July 4, 1959. Bibliography.

"Homologous disease" in animals and lymphoid neoplasia in man have many similar features. It would seem that the wasting, anaemia, and lymphoid depletion observed in both groups of diseases may well be due to a cyto-immunological reaction of lymphoid cells (tumour or homologous) against the usual haematopoietic cells of the host. This theory would explain many of the puzzling clinical features chiefly associated with Hodgkin's disease but also with lymphatic leukaemia and lymphosarcoma at times, and rarely even with reticulum-cell sarcoma and multiple myelomatosis. Some of the evidence which led us to reach the same general conclusion from two quite different approaches has been briefly presented here. While speculations about possible therapeutic applications are of great interest, the present need would seem to be for both more animal and clinical research designed to clarify our ideas about the previously unexplained clinical manifestations of the malignant lymphomas. The recognition of "homologous disease" in mice and auto-immune disease in man may have opened the way.—[Authors' summary.]

126. **The Gastric Juice in Pernicious Anaemia. The Physico-chemical Characteristics of Total Achlorhydria and the Primary Alkaline Secretion of the Stomach.** (Le suc gastrique dans l'anémie pernicieuse. Les caractères physicochimiques de l'achlorhydrie totale et la composition de la sécrétion alcaline primaire de l'estomac)
A. LAMBLING, J. J. BERNIER, Y. NAJEAN, and J. BADOZ-LAMBLING. *Revue française d'études cliniques et biologiques* [*Rev. franç. Ét. clin. biol.*] **4**, 582–592, June, 1959. 9 figs., 30 refs.

At the Gastroenterology Centre, Hôpital Bichat, Paris, the authors have studied the "residual alkalinity" of the gastric juice in 16 patients with pernicious anaemia and in 73 with achlorhydria due to other conditions. The residual alkalinity is defined as and measured by the amount of 0·1 N hydrochloric acid which lowers the *p*H of an achlorhydric gastric juice to 3·5, that is, to the point at which Töpfer's reagent just changes colour and at which free hydrochloric acid begins to appear. They found that in pernicious anaemia the curve of gastric alkalinity during the usual test meal is fairly steady and

notably is not altered after injection of histamine. In contrast, when the achlorhydria is due to conditions other than pernicious anaemia the subcutaneous injection of histamine is followed by a sharp reduction in gastric alkalinity. Of the 73 cases of achlorhydria not associated with pernicious anaemia, only 5 showed true " cellular " achlorhydria—3 of these being cases of cirrhosis of the liver and 2 of gastritis. On the basis of these findings the authors suggest that in pernicious anaemia the stomach has been deprived of its acid glandular function (parietal cells) as well as its peptic (chief cells) glandular function, but maintains its alkaline secretion.

M. C. G. Israëls

127. **The Distribution of the Thalassemia Gene: a Historical Review**

A. I. CHERNOFF. *Blood* [*Blood*] **14**, 899–912, Aug., 1959. 1 fig., bibliography.

128. **Pregnancy in Sickle Cell Anemia, Sickle Cell–Hemoglobin C Disease, and Variants Thereof**

E. M. CURTIS. *American Journal of Obstetrics and Gynecology* [*Amer. J. Obstet. Gynec.*] **77**, 1312–1323, June, 1959. 10 refs.

This paper from the Johns Hopkins Hospital, Baltimore, reviews the obstetric history of 42 negro women with electrophoretically proved abnormalities of haemoglobin, 15 of them having sickle-cell anaemia, 18 sickle-cell–haemoglobin-C disease, 5 sickle-cell thalassaemia, and 4 homozygous haemoglobin-C disease. A total of 77 pregnancies occurred in 31 of these women, but whereas only 9 of the 15 with sickle-cell anaemia became pregnant, 16 of the 18 with sickle-cell–haemoglobin-C disease did so. All the patients with sickle-cell anaemia were anaemic before pregnancy and had experienced crises, and most of them exhibited the characteristic stigmata of the disease. In pregnancy, however, this disease proved to be a much smaller hazard to the mother than did sickle-cell–haemoglobin-C disease, of which the morbidity became apparent only during pregnancy. Thus a crisis occurred in only one case of sickle-cell anaemia during pregnancy and there were no deaths; in those with sickle-cell–haemoglobin-C disease on the other hand half the patients developed increasing anaemia, pulmonary infarction occurred in 6, and there were 4 deaths, these being the only fatalities in the series. No serious maternal complications occurred during pregnancy in the patients with sickle-cell thalassaemia or homozygous haemoglobin-C disease.

Spontaneous abortion occurred in 19% of pregnancies in women with sickle-cell anaemia, and premature deliveries in 29%. The figures for those with sickle-cell–haemoglobin-C disease were 16·3% and 9·3% respectively. Foetal survival ranged from 52% in sickle-cell anaemia to 87% in haemoglobin-C disease. Some aspects of the pathological processes of these diseases in pregnancy are discussed, and the need for accurate diagnosis of the genetic pattern is stressed. Treatment is conservative, emphasis being placed on the maintenance of normal blood levels, by transfusion when necessary.

J. L. Markson

129. **Sickle Cell–Hemoglobin C Disease and Pregnancy Including a Case of Osteomyelitis**

M. A. SACKNER, W. J. DEX, and A. I. KAPLAN. *American Journal of Obstetrics and Gynecology* [*Amer. J. Obstet. Gynec.*] **77**, 1328–1337, June, 1959. 2 figs., 29 refs.

The authors report the detailed clinical, radiological, and laboratory findings in 4 females belonging to one family with sickle-cell–haemoglobin-C disease investigated in Philadelphia General Hospital. A total of 19 pregnancies occurred in these patients, complicated on four occasions by haemolytic crises. This incidence is similar to that reported for sickle-cell anaemia; however, in the present patients only one crisis occurred outside pregnancy, and it is therefore suggested that sickle-cell–haemoglobin-C disease may become symptomatic only during pregnancy. One patient developed acute haematogenous osteomyelitis following a haemolytic crisis which complicated an incomplete abortion. Culture of the pus from an overlying soft tissue abscess, however, gave only negative results. Although chronic osteomyelitis complicating sickle-cell–haemoglobin-C disease has previously been reported, this is apparently the first description of acute osteomyelitis in this condition.

J. L. Markson

130. **The Sickle Cell Diseases in Pregnancy**

J. ABRAMS and I. R. SCHWARTZ. *American Journal of Obstetrics and Gynecology* [*Amer. J. Obstet. Gynec.*] **77**, 1324–1327, June, 1959. 8 refs.

Patients attending the antenatal clinic of the Jefferson Medical College Hospital, Philadelphia, where some 90% of the clinic population is negro, are screened for blood sickling by means of the method of Daland and Castle (*J. Lab. clin. Med.*, 1948, **33**, 1082; *Abstr. Wld Med.*, 1949, **5**, 460). Those in whom sickle cells are found are studied further by paper electrophoresis of the haemoglobin and alkali denaturation. Patients with sicklaemia receive no special treatment; those with sickle-cell diseases are treated conservatively, and during a crisis are given intravenous fluids and blood transfusions when necessary. In this paper 6 cases of sickle-cell disease (patients with haemoglobin SF) and 3 of sickle-cell–haemoglobin-C disease (haemoglobin SC) are described. All 9 patients were delivered spontaneously; there was one stillbirth, but no neonatal or maternal deaths.

J. L. Markson

131. **Effect of Carbonic Anhydrase Inhibitors on the Course of Sickle-cell Disease**

A. B. HENDERSON, E. J. CROCKETT, and C. H. WRIGHT. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **104**, 68–71, July, 1959. 13 refs.

Carbonic anhydrase inhibitors were administered to 4 adult patients having sickle-cell disease. Periods of observation extended from 2 hours to 7 months. No effect of importance could be noted. Variations in *in vivo* sickling, erythrocyte count, and sedimentation rate between cells containing oxygenated and reduced haemoglobins were not significant enough to be indicative of value.—[Authors' summary.]

Respiratory System

132. **Viral Pleurisy and Pericarditis.** (Les pleurésies et les péricardites virales)
J. TURIAF, P. MARLAND, G. BASSET, and P. LORTHOLARY. *Poumon et le cœur* [*Poumon*] **15**, 449–470, May [received July], 1959. 5 figs., 33 refs.

Among 48 cases of lung disease of viral origin (39 due to influenza and 9 to ornithosis) in which the diagnosis was confirmed serologically at the Hôpital Bichat, Paris, during the period 1957–8 there were 11 cases of pleurisy and 3 of pericarditis. The cases of pleurisy were subdivided into 3 groups. (1) Simple pleural effusion; 5 cases, 3 in males and 2 in females aged 20 to 48 years. A serofibrinous fluid was aspirated in all cases, the predominant cells being lymphocytes or endothelial cells or both. In 3 cases the complement-fixation reaction was positive [titre not given] for influenza virus A and in 2 cases for ornithosis [type not stated]. Recovery was complete in all. (2) Encysted fluid. Two males aged 26 and 46 respectively had interlobar effusion, the fluid being serofibrinous in one and greenish in the other, with polymorphonuclear leucocytes predominating. Hirst's reaction was positive for influenza virus A in one case and virus B in the other. Both recovered. (3) Fluid accompanying parenchymatous involvement of the lung was present in 2 males and one female aged 23, 68, and 23 respectively. Radiographs of the lungs showed nodules and reticulation. The fluid was serofibrinous in all cases, the predominant cells being lymphocytes and endothelial cells. Complement-fixation reactions were positive for influenza virus A in all 3. [Titres not given.] All recovered completely. An additional fatal case of pleurisy with involvement of both the lung and pericardium occurred in a 25-year-old woman; post-mortem examination showed a large left-sided haemorrhagic pleural effusion and a serohaemorrhagic pericardial effusion of 200 ml. (A further case is mentioned in which a woman of 55 developed polyserositis (pleural and pericardial) after the major epidemic of influenza had passed and without the typical clinical picture of influenza, but in which the complement-fixation reaction was positive for influenza A). The 3 patients with pericarditis, all female, aged 23 to 56, showed initial cardiac enlargement with bilateral nodular pulmonary opacities in the radiograph. Electrocardiographic changes included flattened and inverted T waves in the chest and limb leads. The complement-fixation reaction was positive for influenza virus A in all 3. Pericardial puncture was not performed, but a clear fluid was aspirated from both pleural sacs in one case. All 3 recovered.

The authors speculate on the pathogenesis of these conditions and mention direct bronchial spread, viraemia, and spread by contiguity as possibilities. They emphasize that pleural and pericardial involvement should always be considered in cases of virus infections of the respiratory tract and that routine chest radiography, electrocardiography, and proof by pleural puncture should not be forgotten. They stress the fact that the course is usually benign and spontaneous recovery the rule in the absence of specific antibiotic treatment. In differential diagnosis tuberculosis, rheumatism, and disseminated lupus erythematosus should always be excluded because their treatment and prognosis are so different.

[This is an interesting paper, but some of its value is lost by the limited laboratory data provided. It serves as a timely reminder of the rarer complications of influenza.] *I. M. Librach*

LUNGS AND BRONCHI

133. **Electrolyte Excretion in Respiratory Failure**
J. TIMONER. *Journal of Clinical Pathology* [*J. clin. Path.*] **12**, 207–209, May, 1959. 1 fig., 10 refs.

Metabolic studies were conducted at Manchester Royal Infirmary on 10 male patients suffering from chronic bronchitis complicated by pneumonitis and congestive cardiac failure. The base-line plasma electrolyte concentrations were measured during clinical recovery and showed in all cases a mild hypochloraemic acidosis with rather low levels of sodium and normal concentrations of potassium. Eight patients were then given ammonium chloride by mouth in a dose of 0·1 g. per kg. body weight and the urine was analysed thereafter. There was an increased excretion of sodium, chloride, and phosphorus, but not of potassium. Hydrogen ion excretion increased by an average of 130%, half of this increase being accounted for by an increased excretion of ammonium ion. The increased excretion of sodium and potassium after ammonium chloride loading was significantly less in these patients than in 10 normal control subjects. In all cases but one the excretion of ammonium bore the normal relationship to urinary *p*H, and this was thought to be because renal glutaminase activity does not increase in respiratory acidosis as it does in metabolic acidosis. *Bernard Isaacs*

134. **Single or Double Segments of the Lung Occupying a Hemithorax: Clinical and Physiologic Evaluation**
R. H. OVERHOLT, E. A. GAENSLER, and J. A. BOUGAS. *New England Journal of Medicine* [*New Engl. J. Med.*] **261**, 10–18, July 2, 1959. 6 figs., 23 refs.

Disease may destroy all but one or two segments of a lung. If resection has to be carried out the choice lies between pneumonectomy and conservation of the single or double segment. The latter procedure may be more difficult technically and more hazardous postoperatively than pneumonectomy, but the extra effort and risk are justified by the contribution made by the conserved segments to pulmonary function. The authors have studied

pulmonary function in 14 patients subjected to extensive pulmonary resection on one or both sides for severe bronchiectasis. In all cases the maximum breathing capacity (M.B.C.), the fast expiratory volume (F.E.V.), and the response to the standard exercise test were determined and bronchospirometry carried out. When signs of obstructive ventilatory insufficiency were present residual volume and pulmonary mixing indices were determined, and the M.B.C. and F.E.V. measured after administration of a bronchodilator aerosol. In 3 out of 5 patients who had a healthy contralateral lung, preservation of one segment contributed 14%, 19%, and 23% respectively to the total oxygen uptake; in 2 patients preservation of two segments contributed 19% and 33% respectively. A sixth patient responded less well because of postoperative pleural complications, the contribution to oxygen uptake being 9%. In 3 cases of contralateral inoperable bronchiectasis the share of total function contributed by the remaining segments increased less than expected, presumably because these segments were also diseased. In the remaining 5 patients subjected to bilateral resections the residual segments contributed a relatively greater proportion of the total ventilation, although oxygen uptake was often low owing to relative over-ventilation. *Bernard J. Freedman*

135. **Effect of the Valsalva Experiment upon Arterial pCO_2, O_2 Saturation, and *p*H in 45 Patients with Obstructive Pulmonary Emphysema**

R. B. SMITH and H. B. HATCH JR. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **53**, 686–692, May, 1959. 3 figs., 16 refs.

Changes in the arterial blood oxygen saturation, carbon dioxide tension (pCO_2), and *p*H following a modified Valsalva manœuvre were measured at the Ochsner Clinic, New Orleans, in 45 patients with mild to severe obstructive pulmonary emphysema and in 100 healthy control subjects. The investigation was undertaken after an increase in the blood oxygen saturation and *p*H and a decrease in pCO_2 had been observed in a patient with obstructive emphysema who developed syncope while performing the manœuvre. It was considered that these changes might be partially responsible for the syncope which sometimes follows a severe paroxysm of coughing. The modified Valsalva manœuvre chosen for the trial consisted in maintaining a maximum inspiration at an oral pressure of 40 to 80 mm. Hg. Blood samples were collected from the brachial artery before and again after 6 and 12 seconds of breath-holding, and finally a third sample was taken after a standard exercise tolerance test.

The results followed one of three patterns, as follows. (1) A slight increase in the oxygen saturation from the normal of 95% to between 96 and 100%, a marked fall in the pCO_2 to 23 mm. Hg, and a corresponding shift in *p*H to the alkaline side; this pattern was observed in all the normal subjects and 30 of the patients, the latter being those with the least degree of emphysema. (2) A decrease in both oxygen saturation and pCO_2, with a rise in *p*H. (3) A decrease in oxygen saturation, a rise in pCO_2, and a fall in *p*H. The changes of Type 1 are attributed to the presence in the alveoli not normally used, except in maximum inspiration, of atmospheric air with its greater oxygen and smaller carbon dioxide content. The transference of the enriched oxygen supply to the pulmonary capillary blood is assisted by the raised mouth pressure present during the Valsalva manœuvre and also by the slowing of the pulmonary capillary blood flow consequent on the reflex slowing of the heart rate which follows a maximum inspiration. The changes of Type 2 are thought to indicate a reduction in the area of the pulmonary capillary bed in patients with severe emphysema, this having a greater effect on the less diffusible oxygen than on the readily diffusible carbon dioxide. The raised pCO_2 in arterial blood present in changes of Type 3 is thought to result from more advanced destruction of the pulmonary capillary bed, as a result of which there is now impairment of diffusion of carbon dioxide in addition to that of oxygen noted in Type 2. The various pulmonary and circulatory mechanisms responsible for these changes are discussed at some length.

It is concluded that the results of the Valsalva manœuvre can be used as a guide to the pathological severity and prognosis of obstructive pulmonary emphysema. *K. M. Hume*

136. **Surgery of Subpleural Blebs: Indications and Contraindications**

F. FERARU and C. S. MORROW. *American Review of Tuberculosis and Pulmonary Diseases* [*Amer. Rev. Tuberc.*] **79**, 577–590, May, 1959. 18 figs., 26 refs.

The terms "bleb" and "bulla" tend to be used indiscriminately and interchangeably by many authors. By definition a bleb is a thin-walled, bladder-like prominence found on the surface of the lung. Miller (*Amer. J. Roentgenol.*, 1926, **15**, 399; 1927, **18**, 42) considered that it was due to the escape of air from a ruptured alveolus into the areolar tissue beneath the visceral pleura. A bulla he regarded as a localized manifestation of generalized emphysema where the interalveolar walls were destroyed by over-distension, thus forming large air spaces within the lung tissue. These bullae communicate with bronchioles and may be so large that they project above the level of the surrounding pleura.

The present authors consider that most surgically treated patients have blebs and not bullae, basing this view on the difficulty they find in collapsing the cysts by compression. The most common and usually the first symptom suggesting the presence of a bleb is the occurrence of a spontaneous pneumothorax due to rupture of the bleb; on the other hand gradual enlargement of blebs on one or both lungs may compress adjacent alveoli so as to cause increasing dyspnoea. Infection and haemorrhage are uncommon, but both have been reported.

The authors consider that surgery, when indicated, should be as conservative of lung tissue as possible, and they describe a simple operation consisting in incision and "unroofing" of the blebs. Any obvious bronchiolar openings are sutured and the cut edges of the blebs approximated over the raw re-expanding lung. The

parietal pleura is rubbed lightly with dry gauze to provoke adhesive reactions. Lobectomy may be indicated where the process is entirely confined to one lobe, but this has not been encountered by the authors. They consider hilar denervation to be unnecessary since pulmonary arterial pressure is reduced by bleb resection alone, and pleurectomy they regard as too radical. Cases selected for operation are those in which the blebs are large enough to cause demonstrable compression of adjacent lung tissue and are considered to be a major factor in the altered respiratory efficiency.

Three cases operated upon at the Veterans Administration Hospital, Wilkes-Barre, Pennsylvania, are described in detail. Four other cases in which surgery was not carried out are equally fully described and the reasons for not performing thoracotomy discussed.

The decision to operate usually rests on determining whether the patient's symptoms can fairly be ascribed to the presence of blebs or bullae; in most cases in which operation was not performed there was other underlying lung pathology, such as pulmonary fibrosis or bronchiectasis, of a degree likely to produce symptoms. The authors consider that the determination of lung compliance is of importance in assessing the response to operation. *W. P. Cleland*

137. **Sputum Examination and the Investigation of "Chronic Bronchitis"**

P. C. Elmes, A. A. C. Dutton, and C. M. Fletcher. *Lancet* [*Lancet*] **1**, 1241–1244, June 13, 1959. 7 refs.

As part of a survey of respiratory symptoms carried out at Hammersmith Hospital, Postgraduate Medical School of London, early morning sputum was collected from 144 postmen and the same number of women postal sorters working in London, the object being to check the validity of answers previously obtained by questionary from the subjects participating in the survey concerning their sputum. One winter and one summer specimen from each subject were collected in sterile universal containers, each specimen consisting of all the sputum produced during the first hour of one day after the subject awoke. Half the subjects were aged between 40 and 49 years and the other half between 50 and 59. The specimens were examined macroscopically and divided into four groups, namely: (1) food and saliva only, (2) pure mucoid, (3) mucoid with diffuse pus, and (4) pure pus; in addition, bacteriological and cytological examinations were carried out. The forced expiratory volume in one second was estimated for each subject, and from this the maximum breathing capacity was calculated.

It was found that half the men and one-quarter of the women produced sputum, and that in more than half the men the winter specimen exceeded 2 ml. About half of the specimens contained pus. Bacteriologically, *Haemophilus influenzae* and *Streptococcus pneumoniae* were the main organisms. Tubercle bacilli were cultured from the specimen of one subject who was, as a result, found to have symptomless pulmonary tuberculosis. A highly significant correlation was established between a heavy growth of *H. influenzae* and the presence of pus in the sputum. There was no relationship between the volume of sputum and the degree of infectivity, but the former correlated significantly both with a reduction in maximum breathing capacity and the amount of sickness absence. These findings correlated well with those of the two earlier parts of the survey—that is, the answers to the questionary mentioned above and the results of investigation into the sickness absence rate.

It is suggested that this method of sputum investigation is a useful adjunct to other methods of survey of chronic non-specific respiratory disease. *K. M. Hume*

138. **Pulmonary Function Tests in Fifty Patients with Bronchiectasis**

N. Cherniack, K. L. Vosti, G. A. Saxton, M. H. Lepper, and H. F. Dowling. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **53**, 693–707, May, 1959. 3 figs., 39 refs.

As part of a 5-year study of the natural history of bronchiectasis being carried out at the University of Illinois College of Medicine, Chicago, tests of pulmonary function have been performed on 50 patients with this disease, the object of the investigation being to assess the physiological defects resulting from bronchiectasis and to determine the effectiveness of therapy in slowing or reversing progress of the disease. The patients, 32 male and 18 female, were aged between 16 and 75 years, 24 of them being over 50, and the disease was bilateral in 41 cases. All had had cough for more than 2 years—60% of them for 10 years or more and 30% for over 20 years. The tests employed included measurement of total vital capacity, forced expiratory volume in one second, maximum breathing capacity, distribution of inspired gas (using the nitrogen wash-out method), venous admixture and diffusion capacity (expressed as the number of ml. of oxygen crossing the alveolar membrane per minute per mm. of mercury pressure gradient, according to the method of Lilienthal and Riley), and alveolar ventilation (by subtracting the dead space, as calculated by the Bohr equation, from the total ventilation). The values obtained were compared with the "normal" values reported by Baldwin *et al.* (*Medicine* (Baltimore), 1948, **27**, 243).

The individual tabulated results show that the vital capacity, maximum breathing capacity, and forced expiratory volume were below 80% of normal in 63, 66, and 80% of the patients respectively. The mean air velocity index was 0·83, indicating that the disease is primarily obstructive, as in asthma or emphysema, rather than restrictive of lung movement, as in pulmonary fibrosis. The area of dead space was increased in 89% of the patients, and it is suggested that bronchiectatic dilatations are more likely to account for this finding rather than the ventilation of poorly perfused alveoli. The fact that there was no relationship between venous admixture, dead space, and the effective alveolar–mean capillary oxygen gradient was taken to indicate that perhaps in some of the present cases enough changes had occurred in the alveolar–capillary membrane to cause a primary defect in diffusion. *K. M. Hume*

Otorhinolaryngology

139. **Primary Quinsy Tonsillectomy**
G. H. Bateman and J. Kodicek. *Annals of Otology, Rhinology and Laryngology* [*Ann. Otol. (St Louis)*] **68**, 315–321, June, 1959. 14 refs.

Among 133 cases of peritonsillar abscess treated by primary tonsillectomy there was only one death, that of a patient already dying from a mediastinal extension of the abscess. Incision of a peritonsillar abscess alone is not considered wise, because the abscess may not lie near the upper pole of the tonsil. It is held that the orthodox incision described in the textbooks would have drained the abscess in only 62 of the 133 cases. In the remaining cases in the series the abscess was found at operation to lie out of reach of the usual incision into the tissue around the upper pole of the tonsil. Primary tonsillectomy is considered to be the treatment of choice in these cases; there are no technical surgical difficulties and postoperative complications are rare.

William McKenzie

140. **Experimental Fractures of the Stapes-footplate in Rabbits: Further Histopathological Studies**
F. Altmann and M. Basek. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **69**, 687–694, June, 1959. 5 figs., 5 refs.

From Columbia University, New York, the authors describe the results of experimental fracture of the stapes footplate in 9 rabbits. They conclude that apart from the danger of middle-ear infection, which they found to be the most common cause of callus formation in these animals, there was a considerable risk of fibrous changes within the labyrinth due to displacement of bone chips into the vestibule, as well as damage to the endosteal lining and serofibrinous inflammation, all causing more or less severe loss of hearing. Although the authors agree that the results of experiments on rabbits, a species particularly prone to middle-ear infection, do not necessarily apply to man, in whom the labyrinth is not so susceptible to infection, they find the excessive enthusiasm for stapes mobilization "somewhat disquieting" and suggest that in some cases the standard fenestration operation or the use of a hearing aid would be safer than "over energetic" stapedial mobilization.

F. W. Watkyn-Thomas

141. **Prosthetics in the Middle Ear: Preliminary Report on the Use of Prosthetics to Reestablish Continuity of the Sound Pressure Transformer of the Middle Ear**
W. H. Harrison, G. E. Shambaugh, J. Kaplan, and E. L. Derlacki. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **69**, 661–666, June, 1959. 10 figs., 12 refs.

The authors describe from the Northwestern University, Chicago, a method of restoring or replacing the bony ossicular chain by the introduction of tantalum or polythene inserts. A new operation, which they term "myringomalleolabyrinthopexy", is suggested for some cases by means of which the Lempert fenestra is linked by a polythene tube to the head of the malleus. It is hoped that this will obviate the two great drawbacks of the fenestration operation, namely, the residual air–bone gap and the slow healing of the large skin-lined cavity, which requires periodic after-care. The cases so treated are as yet too recent to allow of any definite conclusions, but the absence so far of any tissue reaction to these foreign materials in the middle ear has been notable.

F. W. Watkyn-Thomas

142. **Deafness as Part of an Hereditary Syndrome**
L. Fisch. *Journal of Laryngology and Otology* [*J. Laryng.*] **73**, 355–382, June [received Aug.], 1959. 17 figs., 21 refs.

In 1951 Waardenburg (*Amer. J. hum. Genet.*, **3**, 195) described a syndrome characterized by one or more of the following: malformation of the inner angle of the eyelids, congenital perceptive deafness, differently coloured eyes, and a white forelock. In this paper from the Royal National Throat, Nose and Ear Hospital, London, an analysis is presented of 35 cases, with particular reference to the nature and pathology of the hearing defect. This defect varies from moderate to almost total loss of hearing and typically is of the perceptive-loss type, but with low tones more affected than high tones. Histological examination in one patient who died from bronchopneumonia showed that in the cochlea the organ of Corti was absent and the nerve fibres in the spiral canal were markedly reduced. The auditory tracts or nuclei in the cerebral cortex, basal ganglia, brain stem, and cerebellum showed no abnormality.

The author discusses other signs accompanying this syndrome, namely, a particular skull configuration [which he does not describe], patchy pigmentation of the skin, and oesophageal atresia. He considers that hearing and bodily pigmentation have essentially protective functions, and shows that in animals they mature simultaneously. He suggests that an abnormality of the cervical sympathetic nervous system may be concerned in the heterochromia and regards it as significant that the white forelock overlies the site of the median eye and pineal body.

T. A. Clarke

143. **Influences of Semicircular Ducts on Extraocular Muscles.** [Monograph, in English]
E. Fluur. *Acta oto-laryngologica* [*Acta oto-laryng. (Stockh.)*] Suppl. 149, 1–46, 1959. 18 figs., bibliography.

144. **Virus and Rickettsial Diseases in Otorhinolaryngology.** [Monograph, in English]
G. Bellussi, P. Filippi, and L. Scalfi. *Acta oto-laryngologica* [*Acta oto-laryng. (Stockh.)*] Suppl. 147, 1–39, 1959. 24 figs., bibliography.

Urogenital System

145. **The Peripheral Blood Leukocytes in Chronic Renal Insufficiency**
P. Riis and J. Stougaard. *Danish Medical Bulletin* [*Dan. med. Bull.*] **6**, 85–90, May, 1959. 5 figs., 13 refs.

Total and differential leucocyte counts have been determined, at Copenhagen County Hospital, Glostrup, Denmark, in 84 cases of chronic renal failure, due in 72 cases to chronic pyelonephritis and in 12 to other chronic renal diseases. The total leucocyte counts and the neutrophil counts were normal or high and the combined lymphocyte–monocyte counts were low, both relatively and absolutely. There was only a rough correlation between the serum creatinine level and the depression of the mononuclear cells. The investigation has thrown no light, however, on the mechanism by which chronic renal failure influences the leucocytes.

T. B. Begg

146. **The Peripheral Blood Leukocytes in Acute Anuria**
P. Riis and J. Stougaard. *Danish Medical Bulletin* [*Dan. med. Bull.*] **6**, 90–94, May, 1959. 4 figs., 6 refs.

A similar investigation to that reported by the authors above [see Abstract 145] was carried out in 29 cases of acute renal failure due to anuria with almost identical results, suggesting that acute and chronic renal failure influence the circulating leucocytes by the same mechanism.

T. B. Begg

147. **ACTH or Adrenocortical Steroid Therapy of Proteinuria in Adolescents and in Adults**
T. S. Danowski, F. M. Mateer, and A. J. Puntereri. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **237**, 545–558, May, 1959. 13 refs.

The results obtained with ACTH (corticotrophin) or adrenocortical steroids in the treatment of proteinuria in older children and adults are reported in this paper from the University of Pittsburgh School of Medicine. The series included 54 patients (36 male and 18 female, aged 11 to 69 years) and the conditions diagnosed (in 30 cases by percutaneous renal biopsy) were membranous, acute, subacute, and chronic glomerulonephritis, pyelonephritis, intercapillary glomerulosclerosis, lobular nephritis, arteriolar nephrosclerosis, sarcoidosis, disseminated lupus erythematosus, the nephrotic syndrome, and the nephrotic stage of glomerulonephritis. Initially 200 units of depot ACTH was given daily for 28 days, and in many cases treatment was continued with 200 units of ACTH or 200 to 400 mg. of cortisone daily for 3 days a week. Hydrocortisone, prednisone, and triamcinolone were also used.

In 9 patients, mostly in the younger age groups, all abnormal clinical and pathological findings disappeared either after the initial course or during a long period of intermittent therapy. The diagnoses in these patients were membranous glomerulonephritis, nephrotic syndrome, pyelonephritis, lupus erythematosus, and sarcoidosis. In 21 cases the proteinuria decreased, but the clinical and pathological abnormalities did not completely disappear, while in 24 cases there was little improvement. Most of the expected side-effects of steroid therapy were observed, particularly during the initial stage of intensive therapy, anxiety, confusion, or psychosis occurring in 10 cases, major infection in 7, and intra-abdominal complications (including one case of acute pancreatitis and one of bleeding duodenal ulcer) in 6. Permanent diabetes developed in one case and thrombophlebitis of the legs in 2 cases. There were 15 deaths, 4 during the initial course of treatment.

The authors suggest that intermittent therapy is safer and perhaps not less effective than more intensive treatment.

L. Capper

148. **A Clinical Evaluation of the Iodopyracet (Diodrast) Renogram**
M. Serratto, J. T. Grayhack, and D. P. Earle. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **103**, 851–858, June, 1959. 9 figs., 4 refs.

The authors report their experience with the "radioisotope renogram" introduced by Winter and colleagues (*J. Lab. clin. Med.*, 1956, **48**, 886; *Abstr. Wld Med.*, 1957, **21**, 408) in the examination at Northwestern University Medical School, Chicago, of 189 patients with various known disorders of the renal or urinary tract and 33 control subjects without such disease. In this method a small amount of iodopyracet (diodone) labelled with radioactive iodine is administered intravenously and the rate of appearance and disappearance of radioactivity in the renal area thereafter measured by means of externally placed scintillation counters.

The authors found the procedure to be safe, simple to perform, and especially useful in the evaluation of urinary tract disease characterized by obstruction. Bilateral renograms were also helpful in detecting unilateral renal disease and can be used for this purpose in screening patients with hypertension. The renogram was found to be a more sensitive indicator of renal abnormality than the intravenous pyelogram, but in itself is not sufficient to establish the nature of a unilateral renal disease. Lastly, although the radioisotope renogram can give qualitative evidence of impairment of renal function, it is generally less sensitive for this purpose than the established tests of renal function.

G. W. Csonka

149. **Prognosis in the Nephrotic Syndrome. A Study with Particular Reference to the Adult and Older Child**
J. R. Johnson and R. Reader. *Australasian Annals of Medicine* [*Aust. Ann. Med.*] **8**, 200–209, Aug., 1959. 4 figs., 15 refs.

Endocrinology

THYROID GLAND

150. **Iodine Metabolism in Goitrous Cretins**
J. U. GARDNER, A. B. HAYLES, L. B. WOOLNER, and C. A. OWEN. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] **19**, 638–657, June, 1959. 10 figs., 30 refs.

From the Mayo Clinic the authors report a detailed study of 6 goitrous cretins in which the basal metabolic rate and the stable serum iodine, plasma cholesterol, and serum carotene levels were determined in all cases and bone age calculated from radiographs of the hand and wrist. The administration of thyroid extract had been stopped at least 2 months before the investigations. A single dose of 50 to 500 μc. of carrier-free radioactive sodium iodide (^{131}I) was given intravenously and iodine metabolism thereafter investigated by determining the uptake of ^{131}I by the thyroid gland, the thyroid and renal plasma iodide clearance rate, serum levels of total ^{131}I and protein-bound iodine (P.B.I.), together with thyroid scintillation scanning, histological and autoradiographic examination of thyroid biopsy specimens, and chromatography of extracts of the radioiodinated thyroid gland, urine, and serum.

In 3 of these cases they found low serum P.B.I. levels, rapid thyroidal uptake of ^{131}I, and rapid discharge of ^{131}I by the gland after administration of sodium thiocyanate. In one case a small quantity of organic ^{131}I, possibly monoiodotyrosine, was found in the thyroid biopsy specimen, but in the other 2 cases none at all. These last 2 patients, who were siblings, were considered to have a congenital familial defect in the thyroidal conversion of iodide to iodinated amino-acids, as has been previously described. Two other cases showed high serum P.B.I. concentrations, mainly accounted for by radioiodinated mono- and di-iodotyrosine, which were also present in the urine. These 2 patients, also siblings, resembled those described as having a " deshalogenase defect ", but this was not directly tested by administration of tyrosines labelled with ^{131}I. The remaining 2 patients were considered to have only a partial inability to synthesize organic iodine compounds.

K. E. Halnan

151. **The Serum Pattern of Thyroid Hormones in Euthyroidism and Hyperthyroidism**
W. L. ARONS and J. D. HYDOVITZ. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] **19**, 548–556, May, 1959. 3 figs., 17 refs.

In a study carried out at the University of Pennsylvania Hospital, Philadelphia, paper chromatography, in a few cases two-dimensional, was used to separate the organic iodine-containing constituents of the serum of 26 euthyroid and 28 hyperthyroid patients who had just received treatment with radioactive iodine (^{131}I). Small quantities of thyroxine, 3:5:3-triiodothyronine, and other iodine-containing substances were added to the serum before chromatography. The radioactivity at the resulting identifiable carrier sites was used to measure the distribution of ^{131}I in its different organic combinations at varying periods up to 144 hours after its oral administration.

In the sera of the euthyroid patients the main concentration of radioactivity at all time intervals was always in the thyroxine area. Definite radioactivity was found in the triiodothyronine area in only 3 cases. In no specimen of serum was any labelled monoiodotyrosine or diiodotyrosine identified, but in 2 cases there was slight activity at the zonal junction of these two, apparently due to some unidentified substance. The chromatographic findings in the hyperthyroid patients differed in that, although in all cases thyroxine remained the principal constituent, triiodothyronine was seen in the serum of 10 of the 28 subjects and appeared at a much earlier stage after the administration of the ^{131}I. Further, the unidentified substance producing radioactivity at the monoiodotyrosine–diiodotyrosine boundary zone was seen in 8 of the thyrotoxic patients. In neither euthyroid nor hyperthyroid groups were any acetic acid analogues of thyroxine or triiodothyronine found.

The authors conclude (1) that these results provide no evidence to confirm Plummer's hypothesis that an abnormal thyroid hormone is present in thyrotoxicosis, and (2) that it is similarly difficult to implicate excess circulating triiodothyronine as the major aetiological factor in this condition. They acknowledge, however, that the techniques employed can provide only very indirect indications of the pattern of endocrine activity in the tissues.

H.-J. B. Galbraith

152. **Radioiodine Therapy of Hyperthyroidism**
G. E. SHELINE and E. R. MILLER. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **103**, 924–932, June, 1959. 7 refs.

This paper from the University of California School of Medicine, San Francisco, records the results in 431 patients with thyrotoxicosis who were treated with radioactive iodine (^{131}I) between 1945 and 1957, of whom 324 had diffuse toxic goitre, 78 recurrent thyrotoxicosis after subtotal thyroidectomy, and 29 had toxic nodular goitre. Cases of nodular goitre were accepted for treatment with ^{131}I only if surgery had been refused or when there was a reasonably strong ground for refusing operation. Pregnancy was considered an absolute contraindication. The patients with toxic diffuse goitre were of all ages, but those with toxic nodular goitre were all over 40. In most of the cases of diffuse or recurrent goitre, after an initial trial of various methods of dosage, the plan was adopted of giving 0·12 mc. of ^{131}I per estimated gramme of thyroid tissue. Toxic nodular goitre is more refrac-

tory, and here the initial dose was 2 to 4 times the above amount. Treatment was given at intervals of 2 months until the hyperthyroidism was controlled.

It was observed that after a dose of ^{131}I the change in the thyroidal uptake curve sometimes preceded by several weeks any change in the serum protein-bound iodine (P.B.I.) level, or in the patient's clinical condition. Thus the thyroid uptake curve could be in the normal or hypothyroid range while the serum P.B.I. level was still elevated, although the latter decreased later without additional ^{131}I therapy. If the uptake curve remained in the hyperthyroid range at 2 months, a further dose of ^{131}I was usually required. In 408 (95%) of the 431 patients the condition was controlled by the treatment with ^{131}I, this being achieved after only one treatment in 242 cases (59%), namely, in 181 (59%) of those with diffuse toxic goitre, in 50 (69%) of those with post-surgical recurrent thyrotoxicosis, and in 11 (42%) of those with nodular goitre. In the remaining 5% treatment was incomplete for various reasons.

Hypothyroidism occurred in 52 (17%) of successfully treated patients with toxic diffuse goitre, in 16 (22%) of those with a post-surgical recurrence, but in none of those with toxic nodular goitre. The authors found that although the incidence of hypothyroidism can be reduced, this complication probably cannot be entirely prevented by giving smaller doses of ^{131}I. All the patients developing hypothyroidism were given thyroid extract and it was found that recovery of thyroid glandular function can occur in spite of this replacement therapy. In 11 of their patients thyrotoxicosis recurred after treatment; however, after further doses of ^{131}I 9 of them became euthyroid and 2 hypothyroid. The effect of ^{131}I therapy on exophthalmos appeared to be the same as, or slightly better than, that of thyroidectomy: thus of 158 cases in which measurements were made before and after treatment, there was no change in the exophthalmos in 62%, an increase in 24%, and a decrease in 14%.

Kenneth Stone

153. **Anginal Syndrome in Thyrotoxicosis.** (О стенокардии при тиреотоксикозе)
B. P. Kušelevskij and A. M. Gurova. *Клиническая Медицина* [*Klin. Med. (Mosk.)*] **37**, 71–76, June, 1959. 8 refs.

A series of 22 patients with thyrotoxicosis complicated by angina pectoris is described. In this series, in contrast to uncomplicated thyrotoxicosis, the sex distribution was almost equal. Of the 22 patients, 19 were suffering from diffuse primary thyrotoxicosis and 3 from nodular goitre with secondary thyrotoxicosis. The cardiovascular signs included a labile pulse and accentuated second apical sound in all cases, the area of cardiac dullness enlarged to the left in 15 cases, moderate tachycardia in 17, and a systolic murmur in 7. In most cases the blood pressure was near the upper limit of normal and the pulse pressure was increased, while electrocardiographic (E.C.G.) changes were found in all but 2 of the patients. In 3 cases of particularly severe angina there were more marked evening pyrexia and an accelerated erythrocyte sedimentation rate, but no leucocytosis. The basal metabolic rate varied from +25 to +105. The diagnosis of angina was based on the clinical findings, the effects of administration of nitroglycerin, and the E.C.G. changes. From their analysis of the clinical data and the results of treatment the authors divide patients suffering from this condition, which they term the "stenocardial thyreocardiac syndrome" into three groups: (1) those with coronary atherosclerosis and angina who develop thyrotoxicosis; (2) those with thyrotoxicosis who develop angina; and (3) those with thyrotoxicosis and angina who develop small myocardial infarcts.

The pathogenesis of coronary disturbances in thyrotoxicosis includes such factors as intensification of cholinergic reactions, haemodynamic changes which increase the load on the myocardium, an increase in both sympathetic and vagal activity, the direct effects of thyroxine on the myocardium and its nervous apparatus, and disordered and often paradoxical vasomotor reactions. The formation of small areas of necrosis is also a possible factor. Of 10 patients treated conservatively (with thiouracil, sedatives, hypnotics, small doses of iodine, psychotherapy, and hypnotherapy), 7 improved sufficiently to return to work, one relapsed after 6 months, and 2 died, one from acute miliary tuberculosis and one from haemorrhagic pancreatitis. Of the 12 patients treated surgically, 11 were able to return to work, while the remaining patient did well until he relapsed 6 years after the operation, the relapse having been precipitated by severe psychological trauma. *S. W. Waydenfeld*

154. **The Diagnosis and Operative Treatment of Complete Intrathoracic Goitre.** (К диагностике и оперативному лечению полного внутригрудного зоба)
I. I. Zaharov. *Проблемы Эндокринологии и Гормонотерапии* [*Probl. Endokr. Gormonoter.*] **5**, 69–73, May–June, 1959. 2 figs., 8 refs.

Totally intrathoracic goitre is a rare condition—the present author has been able to trace only 41 cases in the available literature. In this paper he presents the histories of 2 cases treated during the years 1954–8, both patients being women in their forties; one case was diagnosed before operation, while the other was at first diagnosed as a dermoid cyst. Such tumours may arise from cells detached from the foetal thyroid gland during its descent to the neck and there forming a supplementary gland, or passing further down with the great vessels to the thorax, coming to rest usually in the posterior mediastinum, while in other cases the whole or part of the thyroid gland itself may be pushed down by the pressure of the cervical muscles into the anterior mediastinum. In the first group transpleural removal is the method of choice, but in the second the transmediastinal approach is preferable.

The diagnosis of such tumours is difficult; it is based partly on the clinical symptoms (pain in the thorax, dyspnoea of increasing degree, palpitation, and sometimes exophthalmos), but mainly on the result of radiological examination. Careful location by radiography, combined with the use of contrast media to determine the relation of the tumour to surrounding structures such as the aorta, trachea, oesophagus, and lung, helps to

differentiate it from benign and malignant thoracic and mediastinal tumours, aneurysms of the aorta or innominate vein, or chronic inflammatory processes in the hilar region. In performing transpleural resection the author employed infiltration anaesthesia, preceded by administration of iodides and bromides and the induction of pneumothorax (twice repeated) to minimize pleural shock at the time of operation. For the transmediastinal resection in the second case he used the same premedication (but without the preliminary pneumothorax), followed by ether–oxygen anaesthesia.

L. Firman-Edwards

ADRENAL GLANDS

155. **The Influence of Hypnotics on Adrenocortical Function.** (Влияние снотворных на функцию коры надпочечников)
K. KYRGE and H. HANSON. *Проблемы Эндокринологии и Гормонотерапии* [*Probl. Endokr. Gormonoter.*] **5**, 39–42. May–June, 1959. 1 fig., 13 refs.

In an earlier study in 1956 the first-named author observed that after the oral administration of hypnotics (usually barbiturates) there was a fall in the absolute number of eosinophils in the peripheral blood. A similar effect was noted in cases of insulin hypoglycaemia and also after the intravenous injection of procaine. As this phenomenon is frequently an index of increased adrenocortical activity the present study was undertaken to ascertain whether hypnotics do in fact increase this activity.

In 33 patients the urinary excretion of 17-ketosteroids and in 17 the urinary excretion of hydroxycorticosteroids was determined following a single dose of 0·5 to 1 g. of thiopentone. In 18 of the 33 cases the urinary excretion of 17-ketosteroids increased by between 25 and 222% (average increase 109%), while in 12 of the 17 cases the urinary hydroxycorticosteroid excretion was increased by between 38 and 200% (average 81·3%). Patients showing little or no increase were mostly those who had reacted poorly to the thiopentone, and in these cases repeated doses often produced a more definite effect, as manifested by increased corticosteroid excretion. It is suggested that lack of hormonal response may be due in part to functional peculiarities in the reaction of the central nervous system, and partly to inertness of the adrenocortical system. The phenomena described are considered to be probably due to a lessening of the inhibiting action of the cerebral cortex by the hypnotic.

L. Firman-Edwards

156. **The Clinical Significance of the Thorn Test (Preliminary Communication).** (Значение пробы Торна в клинике внутренних болезней (Сообщение первое))
B. M. ISKENDERI. *Клиническая Медицина* [*Klin. Med. (Mosk.)*] **37**, 104–108, June, 1959.

In this evaluation of the Thorn test in various clinical conditions, particularly rheumatism, the author reports as follows. The results of the test were positive (reduction of the absolute eosinophil count by 55 to 90%) in all of 10 healthy students who served as controls. In 6 male patients 22 to 60 years of age with Addison's disease the result was as a rule negative (reduction in the count of less than 20%) and remained negative even after treatment, although the eosinophil count did then fall by up to 30%. Results in 60 patients with rheumatism (36 males and 24 females) varied with the severity of the disease and the nature of the treatment. The test result was positive in 24 and negative in 29 patients. The effects of treatment with ACTH and salicylates seemed better in patients with a positive Thorn test result, and at the same time the percentage reduction in the eosinophil count was greater in mild cases, which also responded better and more readily to hormonal treatment. Reversal of the test result from positive to negative occurred in 14 of the 19 cases on the 10th to 15th day of treatment; (reversal in the opposite sense was observed in 2 cases). In the former group, when treatment was interrupted the test results became positive again; it seemed therefore that ACTH therapy in short courses, repeated as necessary depending on the patient's condition and result of the Thorn test, may be more effective than long-term continuous therapy.

The author concludes that the Thorn test can, within limits, be taken as an index of the functional state of the adrenal cortex. The test is positive in health and in mild cases of rheumatism or during its remission, and negative in Addison's disease and in rheumatism during exacerbation or when cardiac failure supervenes.

S. W. Waydenfeld

PANCREAS

157. **The Diagnosis and Treatment of Adenoma of the Insular Tissue of the Pancreas.** (Диагностика и лечение островковой аденомы поджелудочной железы)
F. G. UGLOV. *Клиническая Медицина* [*Klin. Med. (Mosk.)*] **37**, 61–70, June, 1959. 7 refs.

The author discusses the diagnosis and treatment of adenoma of the pancreatic insular tissue. The clinical picture of the disease is dominated by the manifestations of hyperinsulinism, in particular the severe cerebral disturbance, the degree of hyperinsulinism determining the severity of the clinical picture. Usually the onset is relatively slow, beginning with tiredness and somnolence, and later convulsive muscular twitching after strenuous muscular effort, or in women during menstruation. In more advanced cases the combination of hunger with physical effort results in acute cerebral episodes, with loss of consciousness and convulsions. Because of the persistent hunger the patients eat frequently and often become obese. The main symptoms, however, are those arising from the disturbance of the central nervous system (C.N.S.); they include headache, convulsions, irritability, somnolence, episodes of loss of consciousness, and various psychological disturbances. In severe cases the patient may sink into coma followed by death.

Administration of glucose brings about rapid relief of the symptoms, but repeated attacks if allowed to continue may lead to cortical degenerative changes and the development of hemiplegia and dementia. Abdom-

inal pain is frequent, but the predominance of the C.N.S. signs, which do not suggest an abdominal lesion, is a frequent source of diagnostic error. Once hypoglycaemia is discovered estimations of the blood sugar level four times during the day are more diagnostically helpful than a glucose tolerance test. When adenoma of the pancreas is suspected exploratory laparotomy is indicated, but the small tumour is often difficult to find, and moreover the condition is frequently one of diffuse adenomatosis.

The treatment is surgical and, in view of the definite possibility of malignant change, operation should be carried out as soon as possible. Even in cases with distant metastases operation is advised, if only for its palliative effects. The results in non-malignant cases and also in cases shown histologically after operation to be malignant are excellent. The author describes 5 cases, of which 3 were benign, one clinically malignant (in this case the patient survived in relative comfort for 2½ years after the operation), and one histologically malignant (but no evidence of recurrence was found in this case 2½ years after the operation).

S. W. Waydenfeld

158. **Mechanism of Action of Insulin**

A. DUNN, N. ALTSZULER, R. C. DE BODO, R. STEELE, D. T. ARMSTRONG, and J. S. BISHOP. *Nature* [*Nature (Lond.)*] **183**, 1123–1124, April 18, 1959. 4 refs.

In this communication from New York University College of Medicine the authors report the results of an experiment to determine to what extent insulin lowers the glucose concentration in the plasma by increasing glucose utilization by the tissues and to what extent by diminishing its production by the liver. Trained dogs in the post-absorptive state were studied without anaesthesia. The size of the body glucose pool and the rates of production and utilization in the resting state and during periods of changing blood glucose concentration were determined by means of glucose labelled with radioactive carbon (^{14}C-glucose). Trace amounts of ^{14}C-glucose were infused constantly for 2 hours and then, while the infusion continued, trypsin-treated crystalline insulin was administered by continuous intravenous infusion into the jugular vein through a polyethylene tube by means of a constant infusion pump in a dosage from 0·1 to 0·25 unit per kg. body weight over 90 minutes. Blood samples were collected at intervals and the plasma glucose concentration and specific activity determined. From these results the glucose production and utilization were calculated. It had previously been shown by a similar technique that when a single intravenous dose of insulin was given the resulting hypoglycaemia was due mainly to increased uptake of glucose by the tissues. With continuous intravenous infusion, however, the relatively unchanging level of specific activity of plasma glucose showed that the hypoglycaemia which was induced was almost entirely due to increased utilization of glucose, glucose production remaining at about the pre-insulin level. Cessation of glucose production was never observed.

To determine whether endogenous insulin acts in a similar way the secretion of insulin was provoked by the administration of a glucose load. The body glucose pool was labelled with ^{14}C-glucose and the specific activity of the plasma maintained by a constant infusion of labelled glucose as before. At 2 hours a glucose load sufficient to maintain hyperglycaemia for 45 to 60 minutes was given and infusion of the trace amount continued. As shown by the unchanging specific activity of the plasma glucose, glucose production by the liver continued during hyperglycaemia at the same rate as before the glucose load was given, but the rate of glucose utilization was greatly increased. It thus appears that endogenous insulin also lowers the blood sugar level by increasing the utilization of glucose.

The authors had also noted previously that the restoration of the blood sugar level to normal after a single intravenous injection of insulin begins at the lowest point of the glucose concentration curve, when a marked increase in glucose production suddenly occurs. With continuous infusion, however, the extra glucose output was delayed until termination of the infusion, whereupon it occurred suddenly and restored the blood sugar level to normal.

It thus appears that although insulin causes hypoglycaemia by increasing glucose uptake and not by reducing hepatic glucose output, the presence of newly injected exogenous insulin inhibits the animal's hepatic glucose output in response to hypoglycaemia.

John Lister

159. **Action of Prednisone in Insulin-resistant Diabetes**

W. OAKLEY, J. B. FIELD, G. E. SOWTON, B. RIGBY, and A. C. CUNLIFFE. *British Medical Journal* [*Brit. med. J.*] **1**, 1601–1606, June 27, 1959. 6 figs., 21 refs.

In this paper from King's College Hospital, London, 13 cases of severe insulin resistance in which the dose of insulin was more than 200 units daily are described. The presence of insulin antibodies or antagonists in the serum was demonstrated by one or more of the following: interference by serum with the mouse convulsion test; interference with the uptake of glucose by the rat diaphragm; and the response to the passive cutaneous anaphylaxis (P.C.A.) test. In the last-named test various dilutions of the test serum are injected intradermally into a guinea-pig. Some hours later insulin, together with pontamine blue, is injected intravenously. When antibodies are present capillary damage, demonstrated by the leakage of pontamine blue, occurs at the site of the injection. The size and intensity of the blue colour gives an indication of the titre of insulin antibodies.

Of 72 diabetic patients subjected to the P.C.A. test, 13 had antibodies to insulin and of these, 11 were resistant to insulin. Prednisone was given for varying periods to 6 of the resistant patients; 4 who gave a positive reaction to the P.C.A. test before treatment improved rapidly, the insulin requirement falling steeply. In 3 of these the response to the P.C.A. test after treatment was negative. In the remaining 2 cases the dose of insulin required increased during treatment with the steroids; in these cases the result of the P.C.A. test was negative both before and after therapy.

These results suggest that in some cases insulin resistance is due to the presence of antibodies to insulin; in

such cases the insulin requirement is usually near 1,000 units daily and may be considerably reduced by administration of steroids. *A. Gordon Beckett*

160. **Vascular Disease in Diabetes Mellitus: the Relation of Raised Blood Protein-bound Hexose Levels**
I. Kelsey Fry, J. R. Trounce, and C. A. G. Cook. *Diabetes* [*Diabetes*] **8**, 174–178, May–June, 1959. 2 figs., 13 refs.

Many workers have found high levels of glycoproteins in the blood of diabetic patients with vascular complications, while a substance with the staining properties of the glycoproteins has been shown to be intimately related to the histological lesions in the diabetic kidney and retina. It has therefore been suggested that the high concentration of glycoproteins in the blood may lead to their deposition in these organs and that this may be a factor in the development of specific diabetic vascular lesions.

At Guy's Hospital, London, the present authors have studied the level of glycoprotein (estimated as protein-bound hexose by Winzler's method) in the blood of 59 diabetic patients in relation to the presence or absence of each of the main types of diabetic vascular disease—arterial disease, hypertension, renal disease, and diabetic retinopathy. Arterial disease was diagnosed on the basis of a history of angina pectoris or intermittent claudication, the criterion for the diagnosis of hypertension was a diastolic pressure greater than 100 mm. Hg, renal disease was diagnosed if albuminuria was present in a concentration of more than 0·2 part per 1,000, and diabetic retinopathy was considered present when micro-aneurysms were seen. Of the 59 patients, 25 had no signs of vascular disease and 19 had more than one type of vascular lesion. Of the remaining 25, 5 had retinopathy, 5 had albuminuria, 9 had hypertension, and 6 had arterial disease. As a control group, 19 healthy subjects with normal blood pressure were also studied.

In the control subjects the mean protein-bound hexose level was 122·4 mg. per 100 ml. In the 25 diabetics without arterial disease or hypertension the mean level (124·1 mg. per 100 ml.) did not differ significantly from the control value. In the 10 patients with hypertension but without arterial disease, however, the level was significantly higher (138·6 mg. per 100 ml.) and the same was true of the 11 with arterial disease but without hypertension (136·8 mg. per 100 ml.). The presence of diabetic retinopathy or albuminuria alone was not associated with a high glycoprotein level. Since arterial disease and hypertension occur more frequently in older diabetic patients and since the glycoprotein content of the blood normally rises with age, the mean values in two groups of 14 patients matched in pairs for age, one with hypertension or arterial disease or both and the other without these complications, were compared. In the former the value was 143·1 mg. per 100 ml. and in the latter 124·6 mg. per 100 ml., this difference being statistically significant; age was therefore considered not to be an important factor in determining the blood level of protein-bound hexose in diabetic patients with hypertension or vascular disease.

The authors conclude that their findings provide no evidence that the occurrence of retinopathy or albuminuria in diabetes is related to a high level of protein-bound hexose in the blood. When such levels were found in patients with retinopathy or albuminuria they could always be explained by the additional presence of arterial disease or hypertension. *John Lister*

161. **Plasma Glucose Turnover in Humans as Studied with C^{14} Glucose: Influence of Insulin and Tolbutamide**
G. L. Searle, G. E. Mortimore, R. E. Buckley, and W. A. Reilly. *Diabetes* [*Diabetes*] **8**, 167–173, May–June, 1959. 3 figs., 23 refs.

The theory that the hypoglycaemic effect of tolbutamide is due to potentiation of insulin secretion is stated to be "in serious doubt because of the many negative reports concerning a peripheral action for the drug". In order to compare the action of insulin and tolbutamide on the supply of glucose to the circulation the authors, working at the Veterans Administration Hospital, San Francisco, have studied the effects of both compounds on the turnover of plasma glucose in 2 diabetic and 5 non-diabetic subjects. Hepatic and renal function tests gave normal results in all cases, the glucose tolerance curve was normal in the non-diabetic subjects, and neither of the patients with diabetes required insulin in order to prevent ketoacidosis.

Each subject was first studied with insulin and then, after a 5-week interval, with tolbutamide. In each case a light meal was given at 9 p.m., and at 9 a.m. the next day glucose labelled with radioactive carbon (^{14}C) in a dose of 90 μc. was administered intravenously. At least 3 blood samples were then withdrawn at half-hourly intervals and the concentration and specific activity (counts per minute per mg.) of the plasma glucose determined to establish the initial rate of turnover. Insulin (0·05 unit per kg. body weight intravenously and 0·15 unit per kg. subcutaneously) or tolbutamide (0·025 g. per kg. intravenously and 0·065 g. per kg. orally) was then administered, these dosages having been found to cause approximately the same reduction in the blood sugar level and two routes being used to obtain both a rapid and a prolonged hypoglycaemic response. Blood samples were withdrawn at intervals of 8 to 15 minutes for the first hour and of 45 to 60 minutes thereafter, the concentration and specific activity of the plasma glucose being again determined.

Immediately after the administration of insulin the rate of entry of unlabelled glucose into the circulation was reduced to zero in both diabetic subjects and in 2 of the controls, the average duration of this phase being about 30 minutes. During this time the rate of removal of glucose was increased by an average of 151% in the non-diabetic and of 13% in the diabetic subjects and the plasma glucose concentration fell steadily. At the end of this phase the rate of glucose entry increased and the plasma level rose, becoming stabilized at about 50% of the pre-insulin value in both groups. The rate of turnover of glucose was now found to be "remarkably depressed" in all subjects compared with the values observed before insulin administration. After the ad-

ministration of tolbutamide the rate of entry of glucose fell to zero in all 7 subjects for a period which again averaged 30 minutes. But whereas the rate of removal was increased by an average of 44% during this time in the non-diabetic subjects, it remained unchanged in the diabetics. Subsequently, as in the insulin studies, the rate of turnover of plasma glucose was found to be reduced in both groups.

The authors point out that whereas the immediate effects of insulin and tolbutamide on the rates of supply and removal of glucose to and from the plasma were qualitatively similar in the non-diabetic subjects, they differed in the diabetic subjects in that tolbutamide caused no increase in the rate of removal. An acute peripheral action of tolbutamide similar to that of insulin was therefore not demonstrated. On the other hand after the first 30 minutes both insulin and tolbutamide did cause a marked reduction in the rate of turnover of plasma glucose. They suggest that since this rate " is a measure of the simultaneous and equal rates of entry and removal of glucose to and from the circulation, it can be assumed that the rate of removal is dependent on the rate at which glucose can be supplied to the plasma in order to maintain a constant concentration of plasma glucose. Therefore a prime action of insulin or tolbutamide may be to cause the liver to exert a rate-limiting effect on the over-all metabolism of plasma glucose ".

John Lister

162. **The Results of the Treatment with Tolbutamide of 200 Diabetic Patients: a Discussion of Secondary Failure**

J. M. Moss, D. E. DeLawter, and J. J. Canary. *Annals of Internal Medicine* [*Ann. intern. Med.*] **50**, 1407–1417, June, 1959. 6 figs., 9 refs.

It has been noted by various authors that among diabetic patients treated with tolbutamide there have been some who, after an initial good response, later developed persistent hyperglycaemia which did not yield to increased dosage of the drug. In the present paper from Georgetown University Hospital, Washington, D.C., the authors report the results in 200 diabetic patients treated with tolbutamide, of whom 37 had had no previous antidiabetic treatment, 118 had taken insulin in doses varying from 5 to 80 units per day, and 45 had been treated by dietary regulation only. The usual initial dose of tolbutamide was 2 g. per day, this being later reduced or increased (to a daily maximum of 6 g. in a few cases) depending upon the patient's response. No patient had to stop treatment on account of toxic effects.

The early results were classified, by criteria which are described as " excellent " in 41 cases, " good " in 57, " fair " in 58, " poor " in 10, and as failures in 34 (17%). Of this last group of patients showing primary failure, 18 had been taking more than 40 units of insulin per day before starting tolbutamide therapy and 15 of them were under 40 years of age, so that in these cases the result was not unexpected. Within 6 months, however, 14 of the patients showed secondary failure and in a further 18 tolbutamide failed to control the diabetes after proving satisfactory for 6 months. These 32 patients included 8 who were underweight, 14 who were grossly obese, 6 whose diabetes had lasted for longer than 10 years, 6 who were under 40 years of age, and 4 who had previously been taking more than 40 units of insulin per day. In only 5 of these 32 cases had the initial response been good or excellent. Among 90 of the remaining patients who were asymptomatic, non-ketotic, over 40 years of age, near normal weight, and had required less than 40 units of insulin per day before the start of tolbutamide therapy—all these being factors considered to bode well for the success of treatment with tolbutamide—there were 4 primary and 7 secondary failures. Of 3 pregnant female diabetic patients in the series, one failed to respond to tolbutamide, but the other 2 went to term and were delivered of normal babies.

Charles Rolland

163. **A Clinical Comparison of Tolbutamide, Chlorpropamide and Metahexamide in the Treatment of Diabetes**

J. A. Owen Jr. *Metabolism: Clinical and Experimental* [*Metabolism*] **8**, 667–671, July, 1959. 2 refs.

Metahexamide was tried in the treatment of mild diabetes in 19 adult patients at the Veterans Administration Hospital, Washington, D.C. In 12 of the patients the response was good and there was no evidence of toxicity or side-effects. Of these 12 patients, 11 were then treated with tolbutamide and chlorpropamide and all did well on each drug in turn. Comparison of the results with the three drugs in the group of 11 patients showed that the equivalent doses were roughly as follows: tolbutamide 1 g., chlorpropamide 250 mg., and metahexamide 50 mg.

[The value of this trial is limited by the small number of patients.]

K. O. Black

164. **Clinical Evaluation of Metahexamide in the Treatment of Patients with Diabetes Mellitus**

C. Weller, A. Macaulay, M. Linder, and J. D. Tracy. *Metabolism: Clinical and Experimental* [*Metabolism*] **8**, 672–675, July, 1959.

At Grasslands Hospital, Valhalla, and New Rochelle Hospital, New York, the efficacy of metahexamide as an oral hypoglycaemic agent was compared with that of tolbutamide and of chlorpropamide in the treatment of 30 patients with mild diabetes which could not be controlled by diet alone. Metahexamide was found to be effective in nearly two-thirds of the patients. A papular rash developed in one patient; this subsided in one week and the diabetes was subsequently controlled with chlorpropamide. Another patient had dermatitis while taking chlorpropamide and then responded well without side-effects to metahexamide. In 3 patients liver function tests revealed an increase in the alkaline-phosphatase level after 3 months' treatment with metahexamide. Other side-effects were nausea and loss of appetite. The daily maintenance dose of metahexamide varied from 75 mg. to 300 mg. There was no evidence of hypoglycaemic reactions.

K. O. Black

The Rheumatic Diseases

165. **The Diphenylamine Reaction in Rheumatism and Non-specific Infective Polyarthritis.** (О дифениламиновой реакции при ревматизме и инфекционном неспецифическом полиартрите)
V. A. Tihonravov. *Клиническая Медицина* [*Klin. Med. (Mosk.)*] **37**, 41–44, May, 1959. 6 refs.

Destruction of connective tissue leads to the accumulation in the blood of mucoproteins, which can be detected in the serum by means of the diphenylamine reaction. The author, using the colorimetric modification of this reaction described by Ayala *et al.* (*J. clin. Invest.*, 1951, 30, 781) examined the serum of 10 healthy persons, 96 patients suffering from "rheumatism", and 86 patients suffering from non-specific infective polyarthritis. Statistical evaluation of the results showed that in both groups of patients the values obtained, measured in extinction units, were significantly higher than in the control group and that the intensity of the diphenylamine reaction was closely related to the activity and severity of the disease process. *F. S. Freisinger*

166. **A Little Known Metabolic Disorder in Gouty Subjects: Hyperoxalaemia.** (Un trouble humoral méconnu chez le goutteux: l'hyperoxalémie)
A. Mugler. *Presse médicale* [*Presse méd.*] **67**, 1309–1311, June 27, 1959. 29 refs.

Since Garrod first demonstrated (*Trans. med.-chir. Soc. Edinb.*, 1848, **31**, 83) the great increase in the blood uric acid level in gouty patients this finding has tended to dominate the picture. However, the present author, writing from Vittel, points out that the metabolism of oxalic acid may also be disturbed in gouty subjects. In such patients Lœper and Guillaumin have reported an alteration in the ratio between the blood oxalic acid level and the urinary oxalic acid level to between 2:1 and 3·5:1 instead of the normal ratio of 1:2. In a study of 493 patients with hyperuricaemia the present author found hyperoxalaemia to be present in 395 cases (80%), a blood oxalic acid level of 0·5 mg. per 100 ml. being taken as the upper limit of normal. Of the 260 patients with obvious clinical gout, 86·5% had hyperoxalaemia, while in the 233 with hyperuricaemia (but no gout) the incidence was 73%. This finding is considered to be of clinical importance, since a study of lithiasis in 18 hyperuricaemic subjects (with normal blood levels of oxalic acid) revealed that 67% of the calculi contained oxalic acid and only 39% contained uric acid.

Two substances appear to be common to uricaemia and oxalaemia, namely, the aminoacetic acid glycocoll (glycine) and purines. The ingestion of the former has been shown to lead to increased excretion of oxalic acid in subjects prone to oxaluria (but not in normal subjects). Purines also have recently been shown to be associated with increased oxaluria. The author considers that in those cases in which hyperoxalaemia is found to be associated with hyperuricaemia the attacks of gout tend to be aggravated. This, he suggests, may explain the presence of an almost normal blood uric acid level in some gouty subjects in whom the blood oxalic acid level, were it estimated, might be found to be considerably raised. *D. Preiskel*

ACUTE RHEUMATISM

167. **A Controlled Study of Three Methods of Prophylaxis against Streptococcal Infection in a Population of Rheumatic Children. II. Results of the First Three Years of the Study, Including Methods for Evaluating the Maintenance of Oral Prophylaxis**
A. R. Feinstein, H. F. Wood, J. A. Epstein, A. Taranta, R. Simpson, and E. Turkey. *New England Journal of Medicine* [*New Engl. J. Med.*] **260**, 697–702, April 2, 1959. 9 refs.

From New York University College of Medicine comes this further report of the results in 391 children and adolescents who had had unequivocal attacks of rheumatic fever and who have been followed up in a special prophylaxis clinic, the aim being to compare the effectiveness of three prophylactic regimens. An earlier report presenting the results of the first 2 years of this study appeared in 1957 (Wood *et al.*, *New Engl. J. Med.*, **257**, 394; *Abstr. Wld Med.*, 1958, **23**, 200). It is recalled that the three regimens were as follows: (1) 1 g. of sulphadiazine daily by mouth in a single dose; (2) 200,000 units of buffered potassium benzylpenicillin daily by mouth in a single dose half an hour before breakfast; and (3) 1,200,000 units of benzathine penicillin administered by intramuscular injection every 4 weeks. In the first 2 years of the study the attack rates for streptococcal infections per patient-year in the three groups were 24, 20, and 7% respectively, while the rates for recurrence of the rheumatic fever were 2·7%, 4·8%, and *nil* respectively.

In the present study, therefore, an attempt was made to ascertain whether the superiority of parenteral penicillin might have been due in part to the oral prophylaxis not having been faithfully carried out. Two procedures were adopted: (1) a special interview with each patient, on the basis of which prophylaxis was considered "good" if fewer than 5 non-consecutive daily doses had been missed during a month; (2) the patient was supplied each month with a bottle containing a known number of the pills or tablets, prophylaxis being considered "good" if the number of unused pills or tablets returned differed from the expected number by −3 to +4 for penicillin tablets or by −3 to +9 for sulphadiazine tablets. From the results of the interview good prophylaxis was apparently achieved by 75% of patients taking oral penicillin and by 67% of those taking sulphadiazine; by the pill count technique prophylaxis was assessed as good in 55% of patients taking penicillin and

in only 44% of those given sulphadiazine. The accumulative findings for the first 3 years of this study showed that the rates for streptococcal infections per patient-year were now 21, 20·7, and 7·3% respectively, while the recurrence rates of rheumatic fever per patient-year were 1·9, 5, and 0·3% respectively.

The authors' main conclusions are as follows: (1) That 1,200,000 units of benzathine benzylpenicillin given intramuscularly every 4 weeks is more effective in preventing both streptococcal infection and recurrence of rheumatic fever than either of the two methods of oral prophylaxis. (2) The results in the three groups showed little variation even when the oral prophylactic regimen had been faithfully followed. (3) Oral sulphadiazine is approximately equal in effect to oral penicillin in the prevention of streptococcal infections, but is superior to oral penicillin for the prevention of rheumatic fever in patients maintaining good prophylaxis.

Kenneth Stone

168. **Prognostic Significance of Valvular Involvement in Acute Rheumatic Fever**

A. R. FEINSTEIN and R. DI MASSA. *New England Journal of Medicine* [*New Engl. J. Med.*] **260**, 1001–1007, May 14, 1959. 25 refs.

At the Irvington House Prophylaxis Clinic, New York University College of Medicine, 359 patients were observed in their first attack of rheumatic fever and were then followed up for 2 to 9 years (average 4·7 years). They have been examined at monthly intervals and have received continuous antimicrobial prophylaxis.

It was found that definite evidence of cardiac enlargement, congestive heart failure, and pericardial friction rubs occurred almost exclusively in patients who had valvular involvement [this term is fully defined in the paper]. Prolongation of the P–R interval occurred with almost equal frequency in these groups—that is, those with "valvulitis", "probable valvulitis", and "no valvulitis"—but showed no correlation with the subsequent cardiac status. Thus of those who in the acute stage had valvulitis, 67% (86 of 123) ended up with permanent heart disease, as compared with only 25% (13 of 52) of those with probable valvulitis and none out of the 178 who had no valvulitis. It is concluded that the auscultatory findings present during the acute attack of rheumatic fever are of primary importance in predicting the cardiac prognosis.

[The abstracter agrees with these findings and conclusion, subject to the limitations of the medium-term follow-up. Later the situation may not necessarily remain the same.] *John Lorber*

169. **Studies of Acute Rheumatic Fever in the Adult. I. Clinical and Laboratory Manifestations in Thirty Patients**

E. PADER and S. K. ELSTER. *American Journal of Medicine* [*Amer. J. Med.*] **26**, 424–441, March, 1959. 11 figs., 25 refs.

The manifestations of acute rheumatic fever in the adult are described with reference to the findings in 30 patients (12 male and 18 female) aged 21 to 59 seen at Mount Sinai Hospital, New York, between 1952 and 1957. Symptoms in 28 of the 30 cases fulfilled the criteria laid down by Duckett-Jones for the diagnosis of rheumatic fever; in the remaining 2 cases the condition was diagnosed post mortem. Of the 30 patients, 17 of whom were Puerto Ricans, 14 were seen in what was thought to be the first attack, while another 14 were known to have had rheumatic heart disease preceding the acute episode. In 18 there was a history of an upper respiratory infection preceding the onset of rheumatic fever, but none of these had had adequate antistreptococcal treatment. Joint involvement was the most frequent manifestation and was usually a classic migratory polyarthritis. In a series of tables the authors analyse the nature and distribution of the joint involvement and the incidence and various manifestations of carditis, the laboratory findings, and the response to treatment. Details are given of 5 illustrative cases. In strong contrast to the findings in juveniles, none of the adults in this series had erythema marginatum, subcutaneous nodules, or chorea. Rheumatic fever in these adults also differed from that in children in showing a higher incidence of arthritis than of carditis.

E. G. L. Bywaters

170. **Rheumatic Fever and the Thyroid Gland.** (Ревматизм и щитовидная железа)

M. A. JASINOVSKIJ and R. B. PEČENAJA. *Проблемы Эндокринологии и Гормонотерапии* [*Probl. Endokr. Gormonoter.*] **5**, 57–68, May–June, 1959. 2 figs., bibliography.

In this report attention is drawn to the close relationship between acute rheumatism and thyroid dysfunction which has been commented on by many observers from Parry in 1872 to the present day. The results of observations on 1,600 patients have convinced the present authors that a distinct connexion exists between these two disorders. It has often been noted that rheumatism is frequently a precursor of Graves's disease, that acute thyroiditis often occurs in patients with acute rheumatism, and that during the course of Graves's disease in rheumatic subjects the onset of an acute attack of rheumatism may give rise to severe exacerbation of the thyroid symptoms. Vincent, who claimed to have found enlargement of the thyroid gland in some 67% of adult rheumatic subjects, stated as long ago as 1907 that absence of thyroid reaction in rheumatism indicated a poor prognosis. Other authors have described hypothyroidism or in some cases myxoedema as supervening on acute rheumatism.

Among the 1,600 cases of rheumatism seen by the authors at the Therapeutic Clinic, Odessa, between 1935 and 1955, symptoms of thyrotoxicosis were observed in about 10% of cases, this proportion rising in the post-war years to 16 or 17%. Furthermore, of 74 patients with Graves's disease treated at this clinic 9 gave a history of previous rheumatic polyarthritis and 5 had mitral valvular disease, while 4 more had mitral valvular disease without a history of acute polyarthritis. Increased absorption of radioactive iodine was observed in 12 out of 33 cases of rheumatism so tested; while of 20 cases of

acute rheumatism in which the basal metabolic rate was determined, it was raised in all, though clinical symptoms of thyrotoxicosis were found in only 5. A further significant point was that in many of these cases anti-rheumatic treatment alone (aspirin or salicylates) banished or greatly relieved the thyrotoxic symptoms.

The incidence of myxoedema following rheumatism was much lower in this series than that of thyrotoxicosis. Two such cases are reported; in one of these patients, who had two attacks of acute rheumatic polyarthritis, myxoedema developed during pregnancy 4 years after the second attack, while the second patient developed myxoedema 1½ years after the first attack and 2 years before the second; both of these patients also had mitral involvement. While vigorous treatment of the rheumatic condition usually sufficed to allay the symptoms of thyrotoxicosis, repeated relapses of rheumatism in some cases led to the establishment of a stable toxic goitre, necessitating partial or subtotal thyroidectomy. The 2 patients with myxoedema required prolonged thyroid medication—in one case for 10 years. Among the hazards of uncontrolled rheumatism, therefore, must be included thyroid dysfunction, with the possibility of permanent structural and functional change in the gland, this being usually hypertrophic but occasionally atrophic in type.

L. Firman-Edwards

CHRONIC RHEUMATISM

171. **Periarthritis of the Shoulder: a Study of the Disease and Its Treatment**
G. C. LLOYD-ROBERTS and P. R. FRENCH. *British Medical Journal* [*Brit. med. J.*] **1**, 1569–1571, June 20, 1959. 4 refs.

This paper from St. George's Hospital, London, represents a careful study of the results of treatment in 59 cases of periarthritis of the shoulder of a standard minimum level of severity and duration.

It has long been recognized that manipulation under anaesthesia in the acute, irritable phase generally fails to restore movement permanently and often causes an exacerbation of symptoms with a further loss of movement, whereas manipulation at a later and more quiescent phase will generally free movement without risk of recrudescence. The authors wished to discover whether, with the addition of a potent anti-inflammatory agent such as hydrocortisone injected into the joint cavity, manipulation could be carried out successfully in the acute phase and the duration of the disability shortened; 19 cases were treated this way, 25 mg. of hydrocortisone being injected at the same time as manipulation was carried out under anaesthesia and active physiotherapy given subsequently, while 13 cases were treated with 2·5 g. cortisone given orally over a period of one month, together with supervised active movements and palliative physiotherapy. The remaining 27 cases were treated by physical methods, sometimes followed by late manipulation under anaesthesia, but received no steroids.

The use of intra-articular cortisone combined with manipulation under anaesthesia followed by active physiotherapy was found to give considerably more satisfactory results than did the alternative methods of treatment, and the total period of disability was shortened.

W. S. C. Copeman

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The F.II agglutination and the F.II precipitation reaction of Epstein *et al.* (*Proc. Soc. exp. Biol.* (*N.Y.*), 1956, **91**, 235) are based on the interaction between γ globulin (Cohn Fraction II) and the rheumatoid-factor macroglobulin. This reaction may be enhanced by preheating the F.II globulin reactant to 63° C. for 10 minutes. This paper from Roswell Park Memorial Institute, Buffalo, New York, records the estimation of the induced turbidity of this reaction by means of a photronreflectometer. The results were correlated with those of the alligator erythrocyte agglutination and the standard Rose–Waaler haemagglutination reactions.

A total of 58 sera were examined. All of 15 cases of rheumatoid arthritis, in which the haemagglutination reactions were positive, showed increased precipitation activity (turbidity), whereas negative results were obtained in both tests with sera from 26 normal donors and from 15 patients with various other rheumatic and allied diseases, which included dermatomyositis (1) and lupus erythematosus (3), and from 2 with multiple myeloma. Sera from 2 cases of macroglobulinaemia gave negative turbidity reactions with positive haemagglutination reactions. Apart from these cases, representing 3·4%, no false positive results were obtained. *Harry Coke*

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In this paper from the National Institute of Hygiene and the Hôpital Cochin, Paris, the authors review in detail the results of long-term steroid therapy in 100 patients, of whom 6 had ankylosing spondylitis and the remainder rheumatoid arthritis. The mean duration of treatment was 3 years, with a range of one to over 7 years in individual cases. All the patients are now treated with prednisone, although earlier one-third had received cortisone, hydrocortisone, or ACTH. The maintenance dose of prednisone was usually 10 mg. or even less; the authors now consider it preferable to start with a dose of this order rather than one of 15 mg. or more and then reducing. So far as possible aspirin, phenylbutazone, and chloroquine were also given to help to limit the dose of steroid required. However, the value of aspirin in this respect was slight and the authors are "far from confirming" the conclusion reached in a British survey [no reference given] that in the long run aspirin is as valuable as, if not superior to, hormone therapy. The other drugs mentioned were often

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limited in use by gastric intolerance; however, when tolerance is good chloroquine and hydroxychloroquine are valuable, and in 5 patients the use of these drugs ultimately enabled steroid therapy to be withdrawn. ACTH was used mainly to cover withdrawal of steroids, and the authors deprecate its use for intermittent " boosting " of the adrenal cortex.

The patients with rheumatoid arthritis were classified in 4 grades of severity. At the final assessment 63% showed an improvement in grade during treatment, 30% remained static, and 7% deteriorated. [There is no mention of a control group.] Before the start of steroid treatment 10 of the 94 patients were classified as Grade 1 (with little restriction of physical activity); ultimately 44 could be placed in this grade and a further 5 had lost all signs of rheumatoid arthritis. Of the 6 patients with ankylosing spondylitis, 3 showed improvement, mainly in peripheral joints. In regard to side-effects, gastro-intestinal symptoms were common (36%), although proven ulcer occurred in only 6%; these symptoms were not related to the dosage of steroid, but their incidence was twice as high in those with a past history of dyspepsia. Osteoporosis occurred in 16%, resulting in vertebral fractures in 8 and fractured neck of femur in 2 patients. Here the danger was greatest with higher dosage (over 15 mg. daily), length of treatment, degree of immobility, and in women over 60 years of age. Of the 9 deaths in the series, 2 were attributable to steroid therapy (gastric haemorrhage and miliary tuberculosis respectively) and 3 probably so (adrenal insufficiency in 2 cases and amyloid disease in one). The remaining 4 deaths were due to other causes, although possibly aggravated by sudden withdrawal of steroid therapy.

In summing up the authors stress the need for proper precautions in order to achieve the best and very real advantages of steroid therapy. They warn particularly against the dangers of adrenal inhibition and against sudden withdrawal of steroids; they are reserved in their attitude to the new successor drugs to prednisone.

J. A. Cosh

174. **Steroid Therapy and Vascular Lesions in Rheumatoid Arthritis**

R. L. Johnson, C. J. Smyth, G. W. Holt, A. Lubchenco, and E. Valentine. *Arthritis and Rheumatism* [*Arthr. and Rheum.*] **2**, 224–249, June, 1959. 10 figs., bibliography.

The authors of this paper from the University of Colorado School of Medicine, Denver, describe the clinical and necropsy findings in 3 patients suffering from rheumatoid arthritis in whom diffuse arteritis developed. The patients had been receiving steroid therapy for 15 months to 3 years before the onset of symptoms of arteritis, and all had hypercortisonism. The first indication of the presence of arteritis was the development of symptoms and signs of polyneuritis; the patients were febrile.

Gangrene of the finger tips and around the ankles developed in one patient; later, signs and symptoms appeared suggesting arterial occlusion in the heart or brain. A leucocytosis was present, the leucocyte count varying between 18,000 and 53,000 per c. mm. Microscopical examination of tissue removed at necropsy revealed polyarteritis affecting the majority of sections from the visceral and musculo-skeletal systems. The vascular lesions resembled those of polyarteritis nodosa.

Adrenocortical steroids were given in the treatment of 138 patients with rheumatoid arthritis attending the University of Colorado Medical Center in 1957. Of these, 14 developed peripheral neuropathy—9 while receiving steroids and 5 over a period of 1 to 5 months after steroid therapy had been discontinued. Before the onset of peripheral neuropathy 13 patients had received prednisone in a dosage of 10 to 20 mg. daily and one patient had received cortisone. The patients complained of pain and numbness and tingling in the hands and feet. Examination revealed sensory loss of glove and stocking type, weakness of peripheral muscles, and decreased tendon reflexes. Purpuric lesions occurred in 10 of the 14 cases. The authors consider that the peripheral neuropathy noted in these 14 cases was due to arteritis affecting the nutrient arteries of peripheral nerves. After reviewing the literature they point out that although arteritis is known to occur in patients with rheumatoid arthritis who have never received steroids, the incidence of this complication has increased since the introduction of steroid therapy.

C. E. Quin

175. **The Relation of the Rheumatoid Factor Content of Serum to Clinical Neurovascular Manifestations of Rheumatoid Arthritis**

W. V. Epstein and E. P. Engleman. *Arthritis and Rheumatism* [*Arthr. and Rheum.*] **2**, 250–258, June, 1959. 5 figs., 21 refs.

This report describes 9 patients with rheumatoid arthritis who had in common severe deforming disease, subcutaneous nodules, large amounts of circulating rheumatoid factor and significant ischemic skin changes and/or peripheral neuropathy. All 9 had been treated with adrenocortical steroids for periods ranging from 1½ to 5 years. The incidence of subcutaneous nodules and the magnitude of the F II hemagglutination titer in these patients are significantly different from those found in a population of patients with rheumatoid arthritis. No direct correlation was found between absolute endpoint titers and the clinical neurovascular complications. The association of rheumatoid arthritis of stage III or IV, subcutaneous nodules and the presence of large amounts of rheumatoid factor in the serum may constitute a relative contraindication to the use of adrenocortical steroid therapy.—[Authors' summary.]

176. **Changes in the Duration of Vibration Sense in Ankylosing Spondylitis.** (Änderung der Dauer der Vibrationsempfindung bei Bechterewscher Krankheit)

J. Irányi and E. Riesz. *Zeitschrift für Rheumaforschung* [*Z. Rheumaforsch.*] **18**, 211–220, June, 1959. 14 refs.

At the State Institute of Rheumatology, Budapest, the duration of the vibration sense was investigated by means of a tuning fork in 250 patients with various rheumatic disorders. It was found that the vibration sense was prolonged to about twice the normal duration in the majority of 100 patients with ankylosing spondy-

litis. The reason for this finding is not known, but it is suggested that it may be due to irritation of the posterior nerve roots as a result of the narrowing of the intervertebral foramina in this disorder. *G. W. Csonka*

COLLAGEN DISEASES

177. **Antimalarials in Treatment of Sjögren's Syndrome**
J. M. Heaton. *British Medical Journal* [*Brit. med. J.*] 1, 1512–1513, June 13, 1959. 6 refs.

The trial herein reported of antimalarial drugs in the treatment of Sjögren's syndrome was considered worth while because there is evidence that this syndrome is a form of systemic lupus erythematosus, a disease in which antimalarial drugs have a beneficial effect. A total of 15 patients with Sjögren's syndrome were treated at first with chloroquine and later with the reputedly less toxic hydroxychloroquine ("plaquenil"). All the patients had received treatment previously, some for many years, by orthodox methods, but usually there was only slight benefit. The dose of plaquenil was 800 mg. daily for 6 to 12 weeks; if there was improvement the dosage was then reduced to 400 mg. daily. The ocular irritation responded first and then photophobia. Altogether 5 patients were "greatly improved", 12 were "improved", and 8 failed to benefit.

The author states that the period for which it is necessary to continue treatment is not known. In 4 patients the drug was stopped and the eyes became worse within a month, while in one case the eyes remained in a satisfactory state for 3 months after cessation of treatment.

Of 22 patients in the series who had plaquenil, 6 experienced side-effects; these were of a minor nature and resolved rapidly on reducing the dose or withdrawing the drug. *Kenneth Stone*

178. **Factors Influencing the Course and Prognosis of Systemic Lupus Erythematosus**
R. P. McCombs and J. F. Patterson. *New England Journal of Medicine* [*New Engl. J. Med.*] **260**, 1195–1204, June 11, 1959. 6 refs.

Up to 1949 the prognosis in systemic lupus erythematosus was very poor, but the introduction of the L.E.-cell test in 1948 and the almost simultaneous introduction of steroid treatment in 1949 made it difficult to compare later series, even indirectly, with earlier series not treated with steroids because of probable differences in diagnostic criteria. In the present study of 77 cases of systemic lupus erythematosus seen at the New England Center Hospital, Boston, the authors set out to re-examine the course and prognosis of this disease in terms of sex, age, pregnancy, steroid therapy, and certain specific manifestations of the disease process. The analysis included 14 fatal cases first diagnosed before 1949 on clinical evidence alone or with additional post-mortem evidence; the remaining 63 cases were diagnosed between 1949 and 1958, L.E.-cell tests being performed in 20 fatal cases and on 39 patients still living; the results were not available in 4 (fatal) cases. The L.E.-cell test was positive in 13 of the 20 fatal cases and in 11 of the 39 still living patients; in no case, however, was the diagnosis based solely on a positive L.E.-cell test.

There were only 8 males in the series, and of these 6 died compared with 32 out of 69 females. Patients under the age of 21 years at the time of diagnosis did worse (9 out of 15 died) than those over 45 (5 out of 15). In some cases, however, symptoms may have been present for some years before the diagnosis was made. As other workers have found, the presence or absence of renal disease was the most important prognostic feature. Steroid treatment seemed to have no effect on renal involvement, but did suppress the rash, fever, serositis, myocarditis, pneumonitis, and haematological and neurological complications. Pregnancy had little effect once the disease was established. The authors suggest that steroid therapy may have prevented the appearance of renal disease, since only one out of 29 patients so treated later developed renal trouble compared with 3 out of 10 not given steroids. In the untreated series death was due to "toxic" or cardiac causes or to uraemia; of the steroid-treated patients 10 out of 18 died of renal failure and uraemia, while 6 out of 8 died of complications perhaps related to steroid therapy, including infections and gastro-intestinal haemorrhage.

[There is a great deal of useful information in this paper which will repay detailed study.]

E. G. L. Bywaters

179. **Clinical and Roentgenologic Signs of Collagen Diseases Involving the Thorax**
C. M. Nice, A. N. K. Menon, and L. G. Rigler. *Diseases of the Chest* [*Dis. Chest*] **35**, 634–650, June, 1959. 11 figs.

The authors discuss the clinical, pathological, and radiological findings in 109 patients with collagen diseases admitted to the University of Minnesota Hospitals, Minneapolis, between 1942 and 1956. The aetiology is briefly discussed, and the symptoms at onset, laboratory data, electrocardiographic changes, and response to steroid therapy are analysed in a number of tables. The series included 40 cases of polyarteritis nodosa, 37 of disseminated lupus erythematosus, 20 of scleroderma, 7 of dermatomyositis, and 5 of rheumatic pneumonitis. There was pathological confirmation of the diagnosis in over two-thirds of the cases.

The radiological findings are described in some detail. The authors consider that abnormalities occur in the chest during the course of the disease in over 80% of cases. Interstitial pneumonitis, pleural effusion, and cardiac enlargement were common to all five diseases. Bilateral hilar vascular prominence was most often seen in polyarteritis, while interstitial pulmonary fibrosis and emphysema occurred mainly in scleroderma and dermatomyositis; a honeycomb appearance of the mid- and lower-lung fields was present in 20% of cases of scleroderma. Cardiac lesions were more common in disseminated lupus erythematosus and rheumatic pneumonitis and small pulmonary nodules in polyarteritis and scleroderma. Abnormal radiological findings in other systems are also briefly discussed and 12 cases illustrating the value of the x-ray findings in the differential diagnosis are described in detail. *B. Golberg*

Physical Medicine

180. **Physical Fitness of Oarsmen and Rugby Players Before and After Training**
A. W. SLOAN and E. N. KEEN. *Journal of Applied Physiology* [*J. appl. Physiol.*] **14**, 635–636, July, 1959.

Resting pulse rates and fitness indexes by the Harvard step test were ascertained in 100 healthy male University students. The subjects included members of the University rowing and rugby clubs, who were about to undergo systematic training, and a third group of students not engaged in any such activity. The observations were repeated on 58 of the students after a period of 2 to 4 months. The mean resting pulse rates of the three groups were not originally significantly different but after training the pulse rate was significantly lower in the athletic groups than in the controls. At the beginning of the training period the oarsmen and rugby players already had higher fitness indexes than the controls and thereafter they showed significant improvement with training. A significant negative correlation between resting pulse rate and fitness index was found only in the athletic groups.—[Authors' summary.]

181. **Iontophoresis Studies with a Radioactive Tracer**
H. T. ZANKEL, R. H. CRESS, and H. KAMIN. *Archives of Physical Medicine and Rehabilitation* [*Arch. phys. Med.*] **40**, 193–196, May, 1959. 1 fig., 1 ref.

Investigations are reported from Duke University School of Medicine, Durham, N. Carolina, in which, by the introduction of a radioactive tracer into the human subject by ionization, the proportion of a drug administered by this method which is absorbed through the skin into the circulation, the proportion retained in the skin, and its distribution in the various layers of the skin were determined. Radioactive iodine (^{131}I) as iodide ion was used, and before ionization the subject's thyroid gland was saturated with non-radioactive iodine by the administration of 20 drops of a saturated solution of potassium iodide in orange juice. Pads were placed on the anterior surface of each thigh, one being wetted with ^{131}I solution and the other with saline. The negative electrode was applied to the former and the positive to the latter and ionization carried out with a galvanic generator for 30 minutes. The residual activity in the pads was then assessed with a scintillation counter. Activity was also assessed in 24- and 48-hour urine specimens and in the skin by surface counting. To control their experiments the authors carried out similar assessments after application of the pads without iontophoresis, after heating the pads with an infra-red lamp for 30 minutes, and after a combination of heating and iontophoresis.

The mere application of ^{131}I to the skin, with or without the application of heat, did not lead to any significant appearance of radioactivity in the urine. After ionization, however, radioactivity was detected in the urine, the amount present not being significantly increased by the addition of heat. While some radioactivity was found in the skin after simple application, the amount was significantly increased after ionization, though the bulk of the ^{131}I was found to have remained in the pad. The loss of ^{131}I from the pad, however, could not be completely accounted for by the amounts present in the skin and excreted in the urine. The authors suggest that this discrepancy was due to the difficulties inherent in estimating radioactivity in the skin by surface counting. *W. Tegner*

182. **Cervical Spondylosis: Pilot Therapeutic Trial**
V. L. STEINBERG and R. M. MASON. *Annals of Physical Medicine* [*Ann. phys. Med.*] **5**, 37–47, May, 1959. 4 figs., 8 refs.

The authors describe a pilot study of three commonly used physical methods of treatment of cervical spondylosis which they carried out at the London Hospital on 163 patients complaining of neck and/or shoulder pain, or peripheral paraesthesiae attributable to this condition. The treatment regimens were: (1) heat, massage, and longitudinal neck traction given for one-hour periods three times a week for one month (42 patients); (2) the fitting of a felt collar reinforced with plastic, this to be worn as much as possible and especially during sleep (22); (3) neck and shoulder-girdle exercises (6 patients in each class), these being given for half an hour three times a week for one month (29). A fourth smaller control group (7 patients, Group 0) was treated according to the physician's free choice of method. Allocation to the various treatment groups was made by reference to the last digit of the patient's hospital registration number; by chance this method unfortunately resulted in a very uneven distribution, and the authors comment on the advisability of a truly random allocation. The age incidence was highest in the 10-year age group 40 to 49, and was reasonably consistent between the groups. All patients were reviewed after 2 and 4 weeks' treatment, and assessment of the result, being dependent mainly on relief of pain, was entirely subjective.

The results in 146 patients (17 having defaulted) showed that after 4 weeks the felt collar gave the best "improvement" rate (81·8%), the rates in Groups 0, 1, and 3 being 69·2, 70·5, and 71·8% respectively. Group 3 (the exercise group) showed the highest "cure" rate (15·4%), but also the highest defaulter rate (13·3%) and the highest aggravation rate (12·8%). Patients in Group 0 (the "physician's free choice" group) did not do particularly well, and the authors therefore consider that the method of arbitrary selection of treatment employed was quite justified. They also point out that the apparently most effective treatment, that is, the fitting of a collar, is the one most sparing of time for both patient and physiotherapist. They stress, however, that this was a pilot trial only, and much larger numbers of patients, including a placebo group, would have to be studied to provide definite results. *B. E. W. Mace*

Neurology and Neurosurgery

133. **Echo-encephalography: Ultrasonic Rays in Diagnostic Radiology**
D. GORDON. *British Medical Journal* [*Brit. med. J.*] **1**, 1500–1504, June 13, 1959. 2 figs., 10 refs.

The use of ultrasonic rays for medical purposes is reviewed and the physical principles involved described. Diagnostic techniques differ in regard to energy level, focusing, and timing from the techniques used for producing cellular lesions. Descriptions are given of an industrial ultrasonic flaw-detector as modified for medical use and of a comparator—a high-speed change-over switch—permitting the simultaneous use of two ultrasonic probes. The production and significance of echo patterns from the skull and brain are discussed, the large echo originating in the midline being attributed to the septum pellucidum rather than the pineal body. Application to other bodily regions is mentioned.

At its present stage of development the method appears to be of value in examining patients with severe head injuries or other conditions in which angiography or pneumography is inadvisable, and may be more useful than radiography in inoperable and postoperative cases. Its scope should become more widely extended with further improvements in design and longer experience.

J. L. Standen

134. **Spinal Extradural Cysts**
C. R. NUGENT, G. L. ODOM, and B. WOODHALL. *Neurology* [*Neurology* (*Minneap.*)] **9**, 397–406, June, 1959. 4 figs., 31 refs.

The authors of this paper from Duke Hospital, Durham, North Carolina, describe 7 cases of spinal extradural cysts and then discuss the aetiology and symptomatology on the basis of these and 38 cases reported in the literature. Of the 45 patients (27 male and 18 female) 25 were in the age group 10 to 30 years. The average duration of symptoms was 3½ years (range 2 weeks to 28 years). Pain was a symptom in 23 patients; it was severe in patients with cysts in the cervical and lumbar regions and was least common in those with lesions in the thoracic spine. Motor disturbance was more frequent than sensory disturbance. The bladder or anal sphincter was involved in 15 cases. There was radiological evidence of the intraspinal lesion in 32 patients, and in 24 a subarachnoid block was demonstrable. The cysts were in the thoracic area in 30 cases, cervical in 2, thoracolumbar in 4, lumbar in 6, and sacral in 3; all the cervical, lumbar, and sacral lesions occurred in patients over 27 years of age, whereas dorsal lesions were found mainly in adolescents. Kyphosis was present before operation in 8 cases and developed after operation in 3. In 12 cases it was known that the cyst communicated with the subarachnoid space, this communication probably accounting for the fluctuation in symptoms. Of the 45 patients, 20 were " essentially cured " by operation and 10 were improved. The authors consider that the cysts develop slowly, probably as a result of the force of the cerebrospinal fluid pulse, and that this may explain the long history and late neurological defect.

J. E. A. O'Connell

BRAIN AND MENINGES

185. **Drug Therapy of Cerebellar Ataxia and Disorders of the Basal Ganglia, Based on Cerebellar–Striatal Antagonism**
H. KABAT. *Annals of Internal Medicine* [*Ann. intern. Med.*] **50**, 1438–1448, June, 1959. 3 refs.

Writing from the Miriam Hospital, Providence, Rhode Island, the author recalls that previously (*A.M.A. Arch. Neurol. Psychiat* (*Chicago*), 1955, **74**, 375) he showed that patients with cerebellar ataxia and intention tremor exhibit decreased voluntary isometric muscle contraction, while voluntary isotonic contraction (active motion) is relatively unaffected. In contrast, those with lesions of the basal ganglia, such as Parkinsonism, athetosis, and chorea, exhibit the opposite type of imbalance. In discussing the opposing clinical effects of lesions of these organs he advances the theory that the cerebellar discharge facilitates voluntary isometric muscular contraction, whereas one of the functions of the basal ganglia is facilitation of voluntary isotonic contraction. From this he argues that drugs (such as reserpine or chlorpromazine) which cause the temporary appearance of Parkinsonian symptoms should relieve the symptoms of cerebellar lesions, while those which induce signs of cerebellar disturbance might relieve those of basal gangliar lesions.

To test this theory thiopropazate hydrochloride (" dastal "), which produces Parkinsonian signs in relatively small doses, was given in a dosage of 5 to 88 mg. daily to 23 patients—3 with cerebellar ataxia due to arteriosclerosis, one with Marie's cerebellar ataxia, one with ataxia following operation on an acoustic neuroma, and 18 suffering from disseminated sclerosis. Improvement in the cerebellar ataxia was obtained in all but 3 of the patients with disseminated sclerosis, of whom 2 showed no benefit and one became worse. The beneficial effects were produced although signs of Parkinsonism might be absent or minimal, and appeared promptly after administration of the drug. In a second test diphenylhydantoin, a drug which depresses cerebellar function, was administered in doses of 60 to 300 mg. daily to 7 patients with Parkinsonism, 6 with athetosis, and one with progressive chorea following a head injury. All these patients showed significant improvement in isotonic muscle contraction and in muscle power. The author suggests that these observations support the theory of cerebellar–striatal antagonism.

[Some years ago the abstracter also pointed out that, on theoretical grounds, Parkinsonism should be benefited

by inducing a cerebellar lesion. It should be noted that, while the clinical observations in this paper are of interest, the drugs used by the author act primarily on the hypothalamus and reticular formation of the brain-stem, so that the assumption that in the cases described they acted specifically on the basal ganglia and cerebellum is not justified; the effects described might have been produced by their action on the hypothalamus. This would therefore appear somewhat to invalidate the deductions made by the author in favour of his theory.]

R. Wyburn-Mason

186. **Cerebrovascular Disease: II. The Smaller Intracerebral Arteries**

A. B. Baker and A. Iannone. *Neurology* [*Neurology (Minneap.)*] **9**, 391–396, June, 1959. 5 figs., 5 refs.

A study was made in 100 consecutive cases of intracerebral arteries measuring 150 to 500 μ. The chief degenerative change is limited to the adventitia which undergoes proliferation and ultimately replaces the entire vessel wall, causing a fibrotic vessel. Intimal changes or fatty deposits almost never occur. Vascular fibrosis first appears in the third decade of life but is not severe until the fifth decade. Even in elderly subjects, over 50% of the patients will show little or no change within these smaller arteries.

No correlation is found between the changes in these arteries and atherosclerosis in the larger arteries along the base of the brain. In 50% of cases showing severe fibrosis of the smaller arteries, little or no atherosclerosis occurred in the larger vessels. Severe fibrosis of these small arteries was twice as frequent in patients with hypertension or cardiac enlargement. Other somatic diseases were apparently not etiologically concerned in this process.—[Authors' summary.]

187. **Cerebrovascular Disease: III. The Intracerebral Arterioles**

A. B. Baker and A. Iannone. *Neurology* [*Neurology (Minneap.)*] **9**, 441–446, July, 1959. 5 figs., 11 refs.

The normal arteriole is considered to have a maximum diameter of 150 μ. These small blood vessels normally consist of a thin, homogenous, elastic membrane, a muscular media of a few layers thickness and no adventitia, except in a few of the larger arterioles.

The chief degenerative changes in these vessels are limited to the media and consist of a progressive medial fibrosis which ultimately replaces the entire vessel wall. The vessel wall may finally become hyalinized—with a definite thickening of the vessel wall and a narrowing or complete occlusion of the lumen. Parenchymal changes do not result from complete occlusion of these small vessels. This arteriolar fibrosis appears to be a normal physiologic process beginning in the fourth decade of life and increasing in severity with the age of the patient. Various somatic processes, such as hypertension and diabetes, may accelerate this physiologic process so that arteriolar fibrosis may appear at an earlier stage in life.

The frequency and severity of the degenerative changes differ in the cerebral arteries of different size. Any study of cerebrovascular disease must, therefore, consider carefully the artery size and the type of degenerative change characteristic for this size vessel.—[Authors' summary.]

188. **The Natural History of Cerebrovascular Disease**

J. Marshall and D. A. Shaw. *British Medical Journal* [*Brit. med. J.*] **1**, 1614–1617, June 27, 1959. 11 refs.

The authors report the results of a follow-up survey of the 305 cases of cerebrovascular disease (including all cases of primary cerebral haemorrhage, cerebral thrombosis and arteriosclerosis, and occlusion of the internal carotid or vertebral arteries) admitted to the National Hospital for Nervous Diseases, Queen Square, London, over 4 years. Of the 305 patients, 22 died during the first admission; of the 283 survivors, 251 (160 male and 91 female) were traced. The diagnoses in these cases were cerebral haemorrhage (7 cases), cerebral thrombosis (114 cases), diffuse cerebral arteriosclerosis (77), brain-stem thrombosis (30), and internal carotid thrombosis (23). It was found that 65 of the patients with cerebral thrombosis involving one or other of the cerebral hemispheres and 56 of those with diffuse cerebral arteriosclerosis had died, the mortality from both diseases being significantly higher in males. Of the patients surviving an episode of brain-stem thrombosis 14 had died and of those with carotid thrombosis 12 had died, while 2 other patients died from cerebral haemorrhage. The commonest cause of death was a further cerebrovascular accident (69 cases); 29 patients had died from heart disease and 34 from other causes, the cause in the remaining 17 being unknown. Hypertension and increasing age clearly had an adverse influence upon prognosis. It was of interest that of the 102 patients who survived the period of follow-up (4 to 9 years) 95 had had no further cerebrovascular attacks.

The authors conclude that the outlook in cases of brain-stem infarction is less grave than was previously thought to be the case and that diffuse cerebral arteriosclerosis carries the most grave prognosis of all forms of occlusive cerebrovascular disease. Further, cases of cerebral thrombosis fall into two broad groups: in one there is a tendency to recurrent attacks with a fatal outcome, but in the other equally large group the likelihood of recurrent infarction appears to be low and the patients may survive for many years.

John N. Walton

189. **Cerebral Embolism: the Natural History, Prognostic Signs, and Effects of Anticoagulation**

C. E. Wells. *A.M.A. Archives of Neurology and Psychiatry* [*A.M.A. Arch. Neurol. Psychiat.*] **81**, 667–677, June, 1959. 21 refs.

The natural history of cerebral embolism has been studied at New York Hospital (Cornell University Medical College) by reviewing the records of 53 patients, 33 females and 20 males aged from 3 to 76 years, who had suffered 63 embolic episodes and had undergone the usual treatment but had received no anticoagulant therapy. In the patients under the age of 50 years, 36 in all, the diagnosis was made if a sudden cerebrovascular accident had occurred in the presence of rheumatic heart

disease (32 cases) or embolic phenomena had appeared in the absence of evidence of subarachnoid haemorrhage; in those over the age of 50 (17 cases) the diagnosis was based on the occurrence of a sudden cerebrovascular accident associated with auricular fibrillation, recent changes in cardiac rhythm, or multiple embolic phenomena, again without evidence of subarachnoid bleeding. All the episodes were studied in hospital, the great majority of the patients being admitted on the day of onset and in no case later than 6 days after it.

Of the 53 patients, 37 had rheumatic heart disease and hypertension or arteriosclerosis; auricular fibrillation was present in 2 and myxoma of the left auricle in 2, while bacterial endocarditis was present at the time of embolism in 7. Previous embolic episodes had occurred in 20 patients, 9 having had cerebral attacks. Of 41 episodes of which the time of occurrence was known, 25 took place between 6 a.m. and noon, and in 30 (67%) of 45 episodes the incident occurred while the patient was sitting quietly or lying in bed, in 7 cases during sleep; in only 6 cases was it associated with physical effort, and that not severe. Warning symptoms, which were noted at intervals varying from 2 minutes to one hour before onset, were reported by 7 patients; they included numbness in a limb, severe headache, sometimes throbbing, and nausea and vomiting. The actual onset was accompanied by convulsions (8 cases), unconsciousness (19), headache (14), vertigo (3), nausea and vomiting (4), and visual blurring or loss (4). The left cerebral hemisphere was involved in 18 cases, the right in 32, and the brain-stem in 5; the lesion was bilateral in 3 cases. Cheyne–Stokes breathing occurred in 7 episodes and speech impairment in 20. Examination of the blood and cerebrospinal fluid revealed no striking abnormalities except in the patients with bacterial endocarditis. More than one episode occurred in 16 patients, the shortest period between episodes in 2 of these patients being 6 and 17 days respectively.

Death directly due to the embolus or its complications took place from 2½ hours to 2 months after onset in 16 cases. Residual neurological dysfunction was observed after 22 episodes. In general, poor results (that is, death or severely impaired function) were seen in 83% of episodes in patients aged over 50 years, but in only 53% of episodes in those below this age. The result was poor in 25 of the 37 patients with rheumatic heart disease and in 8 of the 9 with hypertensive cardiovascular disease or arteriosclerosis. Of 42 episodes believed to be first attacks, 10 were fatal, while of 15 patients seen in the second attack, 4 died. Poor results were also recorded in 5 of the 7 patients who had premonitory symptoms, in 10 of 16 with severe headache, in 7 of 8 episodes accompanied by seizures, in 17 of 20 associated with unconsciousness, in 12 of 19 with speech impairment, in 6 of 9 with upper and lower facial weakness, and in all cases showing Cheyne–Stokes respiration. Death occurred in 9 of 13 episodes in patients showing progressive disability compared with that at onset. Of 22 cases in which significant recovery began more than 48 hours after onset, the results were poor in 18.

In the second section of this paper the above results are then compared with those in 29 patients (34 episodes) who were being treated with the anticoagulant drugs heparin or dicoumarol before the attacks or who were so treated within 48 hours of onset, but whose general management was otherwise similar. This (the "treated") group consisted of 9 men and 20 women with a mean age of 50 years (compared with 45 years in the "untreated" group) and of whom 27 had rheumatic heart disease. The incidence of seizures, unconsciousness, and Cheyne–Stokes respiration was roughly similar in the two groups. In the untreated group death followed in 16 (25%) of 63 episodes compared with 2 (6%) of 34 episodes in the treated group, a significant difference ($P<0.05$). Severe permanent disability followed 22 episodes in the untreated cases (35%) and in 13 of the treated (40%).

[It should be mentioned that the anticoagulant-treated group would be likely to give the better results as fewer of these patients had prolonged loss of consciousness. Further, no comparison between the 2 groups is made in respect of increase in signs or symptoms or improvement in the paresis within 48 hours after onset. If these three factors were in favour of the treated group, the reduced mortality in this group might have been expected without treatment.] *G. de M. Rudolf*

190. **Anatomical Considerations in the Early Diagnosis of Mesencephalic Lesions.** (Anatomische Betrachtungen zur Früherkennung mesencephaler Prozesse)
G. LIEBALDT. *Archiv für Psychiatrie und Nervenkrankheiten* [*Arch. Psychiat. Nervenkr.*] **199**, 36–59, 1959. 6 figs., 31 refs.

Anatomical and clinical observations made by the author at the University Neurological Clinic, Tübingen, suggest that in the diagnosis of mesencephalic lesions, especially tumours, four successive stages can be distinguished, these being as follows. (1) Pupillary and oculomotor symptoms and impairment of hearing. (2) The appearance of signs and symptoms resulting from narrowing or occlusion of the aqueduct, such as headaches, general irritability, and impairment of memory and concentration, these symptoms being due to the early effects of hydrocephalus. (3) The hydrocephalic symptoms become more marked, with signs of involvement of the cerebral peduncles and paralysis of the lower limbs. (4) In the fourth phase signs of medullary coning appear, especially when there is a tumour of the quadrigeminal area. It is suggested that the manner in which the various groups of symptoms follow each other indicate the direction and speed of progression of the mesencephalic lesion. *E. Stengel*

191. **Hydrocephalus following Subarachnoid Haemorrhage.** (Sull'idrocefalo consecutivo ad emorragia subaracnoidea)
E. RAMELLI. *Sistema nervosa* [*Sist. nerv.*] **11**, 175–192, May–June, 1959. 8 figs., 42 refs.

This paper from the Neuropathological Clinic of the University of Pavia describes in full clinical detail 6 cases seen over the past 5 years in which hydrocephalus developed after subarachnoid haemorrhage. The patients were aged between 40 and 54 years and the author

draws attention to the infrequency of hydrocephalus as a late complication of subarachnoid haemorrhage in adults as compared with children, in whom it is less rare. The rest of the paper is devoted to a review of the various theories and experimental evidence attributing the development of hydrocephalus following subarachnoid haemorrhage to meningeal adhesions resulting from reaction of the meninges to blood in the subarachnoid space and thus causing obstruction to the circulation and absorption of the cerebrospinal fluid. The reasons for the rarity of this complication in adults and its greater incidence in infants are considered, and the clinical features in the author's own cases which were suggestive of hydrocephalus after subarachnoid haemorrhage are pointed out. The author concludes that this complication may be more frequent than is generally believed, and suggests that it should be looked for carefully and if necessary surgical measures undertaken to relieve the hydrocephalus before permanent cerebral damage ensues.

J. B. Stanton

192. **The Value of Photic Stimulation in the Diagnosis of Epilepsy**

S. MELSEN. *Journal of Nervous and Mental Disease* [*J. nerv. ment. Dis.*] **128**, 508–519, June [received Aug.], 1959. 6 figs., 17 refs.

At the Municipal Hospital, Aarhus, Denmark, the author has investigated the response of 1,366 patients to photic stimulation during electroencephalography (EEG). By criteria which are defined the patients (735 males and 631 females of all ages) were divided into three groups: (1) 356 with symptomatic epilepsy, (2) 445 with cryptogenic or idiopathic epilepsy, and (3) 565 in whom epilepsy was only suspected, these being patients who had had atypical attacks, in many cases on only one occasion; only patients whose routine EEG showed no paroxysmal abnormalities were included in the study. The EEG records were classified as normal, diffusely abnormal (that is, with diffuse slow activity below 6 c.p.s.), or focal (those showing focal slow activity below 8 c.p.s.), and the result of photic stimulation was considered to be positive only when paroxysmal abnormalities such as spike-and-wave discharges, bilateral paroxysmal discharges, or focal spikes were produced.

Paroxysmal activity was excited by photic stimulation in 150 cases (11·2%), a positive response being more common among patients with cryptogenic epilepsy (24·7%) than in those with symptomatic epilepsy (6·7%), while in the cryptogenic group paroxysmal responses were obtained more frequently in females than in males. In 44 cases photic stimulation produced conspicuous EEG changes of two types, myoclonic jerks (9 cases) or diffuse EEG irregularities with low-voltage spikes (35 cases), but these changes were regarded as non-specific. Photic stimulation was most effective in the younger patients in all groups and in patients with abnormal routine EEG records. The most effective flicker frequencies were those of 12 or 14 per second; electronic triggering of the flicker frequency from the EEG rhythms in the occipital lobe increased the number of positive results.

The author discusses the value of photic stimulation in the diagnosis of epilepsy and compares his results (11·2% of positive responses) with those reported by others, which have ranged from 10 to 20%. He points out that the present study afforded no measure of the specificity of the procedure since there was no control group.

J. B. Stanton

DEMYELINATING DISEASES

193. **Multiple Sclerosis as an Incidental Complication of a Disorder of Lipid Metabolism: I. Close Resemblance of the Lesions Resulting from Fat Embolism to the Plaques of Multiple Sclerosis. II. A Survey of the Geographical, Clinical and Biochemical Evidence; the Significance of Endogenous Fat Embolism. III. Treatment with Heparin of Acute Exacerbations of the Disease**

C. B. COURVILLE. *Bulletin of the Los Angeles Neurological Society* [*Bull. Los Angeles Neurol. Soc.*] **24**, 60–105, June, 1959. 12 figs., bibliography.

In the first part of this paper from the College of Medical Evangelists, Los Angeles, the pathological findings in the brain of a woman who died from fat embolism 5 days after a motor accident are described. The brain showed multiple scattered focal areas of demyelination throughout which bore some resemblance to the plaques of disseminated (multiple) sclerosis (D.S.). In addition there were numerous small pin-point and petechial lesions typical of fat embolism. The main difference between these lesions and those of D.S. was that several of the larger ones showed evidence of frank liquefaction, which is a rare feature of the definitive plaque. It is stated that the myelin loss was selective and that the axis cylinders were intact [but the illustrations are not adequate to allow the reader to assess this very important feature for himself].

While the author does not regard this case as an example of D.S., he puts forward the idea that the plaques of that disease might be considered to be the end result of a similar ischaemic process. He emphasizes that the loss of myelin and oligodendroglia in D.S. is merely an indication of the relatively greater susceptibility of these elements to the damaging process, which might well be ischaemia. Moreover, the scattered, quasi-symmetrical distribution of the plaques is compatible with an embolic origin, and lipid material would be the most likely cause of such embolism because of its ready subsequent disappearance.

In the second part of the paper he extends this line of reasoning. He reviews the observations of Swank on the geographical prevalence of D.S. among peoples consuming a high fat diet and emphasizes the loss of weight in patients with the disease which, he claims, cannot be adequately explained on dietary grounds. Next he considers the behaviour of chylomicrons and notes their tendency to form sizeable clusters, particularly after a heavy meal. The occurrence of alterations in the lipid constitution of the serum in D.S. and the finding also of increased serum lipase activity suggests to the author that there may be some underlying disorder of lipid metabolism in this disease. He cites from the literature several

other conditions in which non-traumatic fat embolism has been described. Finally he defines his lipid theory of the pathogenesis of D.S. on the basis of this brief review of the evidence.

In the third part the author describes an attempt to determine whether an improvement in the neurological condition in D.S. would result from treatment with an antilipaemic agent. Courses of heparin in small doses were administered intravenously to 7 patients during an acute exacerbation of the disease, the drug being given 4 times a day for several weeks. The result is reported as " good " in 4 cases, " incomplete " in 2, and a failure in one case. [No objective methods were used for assessing the rate of improvement, nor was any comparison with control cases made at the relevant times.] The follow-up period was less than one year in all cases.

[In view of the strong *post hoc ergo propter hoc* flavour of the author's arguments, the uncritical survey of the problems, and the lack of proper control of the therapeutic venture it is necessary at present to view this treatment as quite empirical and of unproven value.]

J. B. Cavanagh

194. **The Effects of Induced Hyperthermia on Patients with Multiple Sclerosis**

O. A. NELSON and F. MCDOWELL. *Journal of Neurology, Neurosurgery and Psychiatry* [*J. Neurol. Neurosurg. Psychiat.*] **22**, 113–116, May, 1959. 4 refs.

The authors have previously reported (*A.M.A. Arch. Neurol. Psychiat.*, 1958, **79**, 31) that patients with multiple (disseminated) sclerosis frequently develop new transient neurological signs on exposure to heat or during treatment with fever therapy. They also showed that patients with other neurological disorders tended to develop such exacerbations, but in general they were less sensitive in this respect than the sclerotic patients.

In the present study, which was undertaken at Bellevue Hospital (Cornell University Medical College), New York, in an attempt to determine the exact temperature at which these additional neurological signs develop, 8 patients with disseminated sclerosis in remission and 6 in exacerbation were exposed either to infra-red lamps or to hot baths, during which the skin and rectal temperatures were recorded by means of thermocouples; of these 14 patients, 8 had admitted to having previously experienced weakness in a hot bath. As a result of the heat treatment 13 of the 14 patients developed new neurological signs when the body temperature was raised by between 0·3 and 2·7° F. (0·17 and 1·5° C.), mean $1·3 \pm 0·7$° F. ($0·7 \pm 0·4$° C.). These signs consisted chiefly in a decrease in visual acuity, nystagmus, and disturbances of ocular movements. They tended to disappear while the body temperature was still above that at which they first appeared, and in 2 cases even while the temperature was still rising. These neurological changes could not be correlated with any change in the blood pressure or with the duration of exposure to heat. To account for this phenomenon the authors suggest two possibilities—either the direct action of the increased temperature upon the damaged tissue or the release of humoral substances acting upon the conducting elements in the demyelinated plaques. [The possibility that redistribution of the blood in the body could lead to transient ischaemia in some areas was apparently not considered.]

J. B. Cavanagh

195. **The Cholesterol and Cholesterol Ester Content of Cerebrospinal Fluid in Patients with Multiple Sclerosis and Other Neurological Diseases**

J. B. GREEN, N. PAPADOPOULOS, W. CEVALLOS, F. M. FORSTER, and W. C. HESS. *Journal of Neurology, Neurosurgery and Psychiatry* [*J. Neurol. Neurosurg. Psychiat.*] **22**, 117–119, May, 1959. 6 refs.

At Georgetown University School of Medicine, Washington, D.C., the cholesterol and cholesterol ester levels in the cerebrospinal fluid (C.S.F.) of 6 (control) patients without neurological disorder, 13 patients with disseminated sclerosis, and 34 with other types of neurological disease were determined by extraction and subsequent chromatographic separation of free and ester cholesterol, these being then estimated colorimetrically. The γ-globulin content was also determined in the C.S.F. of the patients with disseminated sclerosis by the zinc sulphate precipitation method. In 5 of these patients the C.S.F. cholesterol ester level was above 60% of the total cholesterol content, whereas in none of the other cases was this figure surpassed. No exact correlation between ester percentage and severity of the disease was apparent, but in general the more severe cases of the disease tended to show higher C.S.F. cholesterol ester levels.

J. B. Cavanagh

196. **Thyroid Function in Disseminated Sclerosis.** (О функциональном состоянии щитовидной железы у больных рассеянным склерозом)

A. L. VALTNERE. *Журнал Невропатологии и Психиатрии* [*Ž. Nevropat. Psihiat.*] **59**, 523–524, No. 5, 1959. 2 refs.

The author has investigated thyroid function in 5 female and 9 male patients aged 23 to 48 suffering from disseminated sclerosis by determining the uptake of radioactive iodine (^{131}I) by the thyroid gland. The ^{131}I (dose 2 μc.) was given orally in the form of a solution of sodium iodide and uptake measured by Geiger counter at 30, 60, 90, and 120 minutes and 24 and 48 hours, the result being expressed as a percentage of the ingested dose. In 9 cases a second similar investigation was carried out after an interval of 2 weeks.

In the first investigation the uptake of ^{131}I in 10 cases was higher than 30%, in 7 being as high as 60·8 to 86%, while in 3 it was within normal limits. The maximum uptake occurred at 24 hours in 9 cases, at 48 hours in 3, at 2 hours in one, and at one hour in one. In the second investigation 6 of the 9 patients showed an increase in uptake ranging from 5·2 to 23·8% above that in the first investigation, while the other 3 showed a decrease of 17 to 22·7%. Maximum uptake was noted at 24 hours in 7 cases. In 2 cases (one in each investigation) a fall in uptake was succeeded by a secondary rise. Thus thyroid function was increased in the majority of these patients, but no relation could be demonstrated between the degree of thyroid activity and the age of the patient or the severity of the disseminated sclerosis.

Margot G. Dunlop

Psychiatry

197. **Twin-like Behavior in Non-twins: a Clinical Report of Two Poliomyelitis Patients**
H. H. BREWSTER. *Psychosomatic Medicine* [*Psychosom. Med.*] **21**, 193–203, May–June, 1959. 1 ref.

A clinical study is reported from Western Reserve University, Cleveland, Ohio, of 2 married female patients who suffered from poliomyelitis with respiratory and limb paralysis of nearly identical distribution and severity. These patients were strangers to each other until they met in hospital, where they were exposed to the same external environment. The formulation of the problem is in psychoanalytical terms. Satisfactory recovery in both cases began to occur only when they were placed in a two-bedded ward under the care of the same physicians, nurses, and physiotherapists.

The psychiatric study was begun during the 4th month of the patients' " partnership ", and was instigated by the medical staff, who felt that the patients were afraid to relinquish mechanical respiratory assistance. Initially, information was obtained from the attending physicians, nurses, and physiotherapists as to the patients' reaction to their disease, to the staff, and to each other. Latterly, during the 6th to 8th month of their life together, the author conducted personal interviews with the patients in succession.

The patients were aged 27 and 33 years respectively; each had been the middle child of 3 siblings, and each displayed a number of long-term phobic symptoms. The younger patient during childhood had had a strong identification with a younger sister, while the other patient had had a competitive relationship with an elder sister. Both patients became profoundly dependent upon the tank respirator, fearing that if they left it they would be totally unable to breathe. Although they were not twins they behaved towards each other as if they were. While in some respects their behaviour represented a reactivated sibling rivalry, their libido was, in fact, largely directed upon each other, and they regarded themselves as a team or as a unity. This twin-like behaviour is postulated as constituting an ego defence against (1) the psychophysiological helplessness engendered by their condition, and (2) the separation from normal libidinal objects resulting from hospitalization.

A. Balfour Sclare

198. **Psychopathology of Memory.** (Psychopathologie des Gedächtnisses)
A. ADAMS. *Fortschritte der Neurologie, Psychiatrie und ihrer Grenzgebiete* [*Fortschr. Neurol. Psychiat.*] **27**, 243–262, May, 1959. Bibliography.

This communication from the University of Freiburg surveys the work on disturbances of memory carried out during the last 12 years. The author first considers the various theories of mnesic dispositions, this being followed by interpretations of memory function on the basis of *Gestalt* psychology. Next, memory structure and the neurophysiological correlates of remembering are discussed. Methods of examination of memory, and in particular failure of memory, are described, and the literature on amnesic states and their cerebral pathology briefly reviewed. Finally memory is considered in relation to time experience.

[This is a very comprehensive and most useful survey.]

W. Mayer-Gross

199. **The Theory of Movement Interpretation in the Rorschach Test.** (Zur Theorie der Bewegungsdeutung im Rorschach-Versuch)
H. H. KORNHUBER. *Fortschritte der Neurologie, Psychiatrie und ihrer Grenzgebiete* [*Fortschr. Neurol. Psychiat.*] **27**, 276–291, May, 1959. Bibliography.

The Rorschach test is widely used in psychological and psychiatric practice all over the world. However, apart from the refutation of its usefulness *in toto* very little critical appraisal in detail has been published. The present author, writing from the University of Freiburg, has concentrated on the problem of projection of movement into the ink-blot patterns of which the test is composed. He recapitulates the history of the interpretation of these movements, quotes Rorschach's own views, criticizes the present theories, and discusses the idea of " projection " and its relation to knowledge and phantasy. Finally he offers an interpretation of movement from the point of view of *Gestalt* psychology, with frequent references to the methods of interpretation of the Rorschach test as a whole. *W. Mayer-Gross*

200. **An Analysis of 133 Homosexuals Seen at a University Student Health Service**
F. MENDELSOHN and M. ROSS. *Diseases of the Nervous System* [*Dis. nerv. Syst.*] **20**, 246–250, June, 1959. 38 refs.

The authors survey the cases of 133 students with homosexual problems who were seen at the Psychiatric Clinic of the Student Health Service of the University of California at Los Angeles in the period 1946–57. They constituted about 3% of the cases dealt with by the clinic in that period. Of the 133 students in question, 81 men and 20 women stated that they were " currently engaging in or had previously engaged in homosexuality " —that is, physical contact with others of their own sex " for the conscious purpose of sexual gratification ". The remaining 28 men and 4 women reported strong homosexual impulses but no overt acts.

After collecting and analysing a mass of data the authors concluded that there were few respects in which these 133 students differed from the non-homosexual students seen at the clinic. The average scholastic performance of the women homosexuals was substantially better than the average for women undergraduates

of the university, and the proportion graduating was double the usual figure. [Details not given.] The male homosexuals were about average in academic performance, but the proportion " in graduate work " was smaller and that studying applied arts, and especially theatre arts, larger than in the rest of the student body. The effect of psychotherapy on 15 of the overt male homosexuals and 5 of the overt female homosexuals was studied and compared with that on a similar group of non-homosexuals treated for an equal period. The results in the two groups were alike, 4 patients in each being considerably improved. Of the 3 homosexual males who were improved one, aged 26, became " continent " after 15 months of treatment and graduated successfully. The second, aged 17, had 28 sessions of psychotherapy and gave up overt acts, but continued to keep company with homosexuals. The third, aged 19, after 64 sessions over 2 years still had homosexual impulses, but ceased overt acts. The ages of 2 of these men were well below the median age of the overt male homosexual group, which was 24 years. Of the 4 improved patients, 3 had indulged in fewer than 10 overt acts since the age of 16, whereas among the other 21 under treatment, all but one had indulged more frequently.

On the basis of these figures the authors " tentatively conclude " that young age and little overt behaviour are good prognostic signs in homosexuality. They consider that " the most important finding was the equal efficacy of psychotherapy in treating homosexual and non-homosexual psychiatric patients ". *D. J. West*

MENTAL DEFICIENCY

201. **A Controlled Experiment of Glutamic Acid Therapy: First Report Summarizing Thirteen Years of Study**
F. T. ZIMMERMAN and B. B. BURGEMEISTER. *A.M.A. Archives of Neurology and Psychiatry* [*A.M.A. Arch. Neurol. Psychiat.*] **81**, 639–648, May, 1959. 36 refs.

The authors report from Columbia University College of Physicians and Surgeons, New York, a comparative trial of the effects of glutamic acid which was carried out on 350 retarded patients ranging in age from 4 to 15 years (59% being boys), of whom 150 were treated with glutamic acid, 150 with reserpine, and 50 with a placebo. The groups were closely matched in respect of age and intelligence quotients, the latter being 59, 61, and 61 in the three groups respectively. The dosage of glutamic acid was increased gradually from between 0·15 and 0·3 g. daily according to age up to that which was considered to be an effective dose. The initial dosage of reserpine was small, but was increased uniformly also until a clinically effective dose was reached, the daily dosage range being 0·2 to 1·75 mg. (average 0·75 mg.) divided in 3 doses. The Stanford–Binet test (Form L) and either the Merrill–Palmer or the Pintner–Paterson performance test were given before and after 6 months of treatment. Observations of behaviour were made by both the psychologist and the neuropsychiatrist.

There were no significant gains in the results of the performance tests in any group, but a significant mean gain of 5·49 points in the Stanford–Binet test occurred in the glutamic acid group, the mean corresponding gains in the reserpine and control groups being 1·31 and 1·02 points respectively. In respect of a large number of behavioural traits rated clinically there was improvement in 127 (64%) after 6 months' glutamic acid therapy, in 57% after a similar period of reserpine, and in 32% of the control group. Glutamic acid treatment was followed by improvement chiefly in the form of lessened distractibility, hyperactivity, unresponsiveness, slowness, and depression, whereas reserpine therapy produced most effect in patients who were anxious, tense, insecure, irritable, negativistic, and hyperactive. Children out of control and confused or those who were psychotic showed more improvement with reserpine, but those who were shy, withdrawn, and quiet responded better to glutamic acid. Reserpine caused more pronounced and more frequent side-effects than did glutamic acid, these consisting mainly in gastric distress and hyperactivity due to overdosage. The authors postulate that glutamic acid appears to form part of the Krebs cycle and that it may have a direct effect upon the nervous system.

G. de M. Rudolf

202. **Analysis of Behavior Patterns following Glutamic Acid Therapy**
F. T. ZIMMERMAN and B. B. BURGEMEISTER. *A.M.A. Archives of Neurology and Psychiatry* [*A.M.A. Arch. Neurol. Psychiat.*] **81**, 649–657, May, 1959. 1 fig., 14 refs.

This further study of the effects of glutamic acid [see Abstract 201] was carried out on 464 private patients of an average age of 9½ (range 3 to 16) years, 58% of them being boys. The verbal I.Q. ranged from 31 to 96. At the beginning of treatment and again at 6, 12, 18, 24, and 30 months the same tests as above, this time with the addition of the Rorschach test, were administered. Ratings of behaviour were recorded as before by the psychologist and the neuropsychiatrist. The dosage of glutamic acid was also as previously described.

The average verbal I.Q. for the group was raised by 5·64 points in 6 months, by a further 0·74 of a point after 1 year, and by a total of 7 points after 2½ years, all these differences being statistically significant. The mean I.Q. as judged by the performance tests was raised by between 3·12 and 5·67 points over 2½ years, but these figures were not significant. A rise in I.Q. of from 1 to 23·99 points occurred in 84% of patients. No correlation was found, however, between increase in test scores, intelligence level, and success of glutamic acid therapy. In 68 psychotic patients Rorschach test scores showed no change, and there was also very little alteration in the results of either verbal or performance tests; the exclusion of this group from the analysis improved the mean results considerably. Improvement in the verbal test score but not in the performance score occurred among 46 patients with organic neurological involvement. On the whole, improved scores were due to " abstract " rather than " concrete " thinking. In many of these cases improved form perception and reduction in reaction time were recorded. Improved changes in personality, as judged by the Rorschach test results after 6 months' treatment,

were as follows: in F (form perception) 36%, F.M. (animal movement) 22%, C.F. (colour form) 18%, M (human movement) 12%, and F.C. (form colour) 7%. Improvement in behaviour as assessed by the psychologist occurred in 56% of cases after 6 months' treatment and in 55% as assessed by the neuropsychiatrist. The proportions showing improvement varied with various behaviour characteristics; thus of shy, withdrawn, quiet children, 68% showed improvement; of slow and depressed patients, 66%; of easily distractible patients, 57%; of those who were aggressive, wilful, and hyperactive, 56%; of the anxious, tense, and insecure, 42%; and of those out of control or confused, 21%, but overlapping in all traits occurred with regard to improvement. A positive correlation between a rise in I.Q. scores and improvement in behaviour (biserial r=0·45) was found. *G. de M. Rudolf*

SCHIZOPHRENIA

203. **A Preliminary Experiment on Paranoid Delusions**
M. B. SHAPIRO and A. T. RAVENETTE. *Journal of Mental Science* [*J. ment. Sci.*] **105**, 295–312, April [received July], 1959. 1 fig., 18 refs.

The authors describe a study undertaken to elucidate the question whether rational discussion could change the strength of delusions in a patient. The subject was a 38-year-old man who had been suffering from paranoid and depressive delusions for about 5 years. The diagnosis was paranoid schizophrenia, but during his stay in hospital he had an episode of acute depression which cleared up after 8 treatments with electric convulsion therapy (E.C.T.) given over a period of 41 days. [It is not stated whether this treatment was given before or after the authors' experiment.]

The patient had two kinds of delusions: (1) delusions of guilt about professed sexual misdemeanours (homosexuality and bestiality) and about having been a conscientious objector during the war; and (2) paranoid delusions concerning his wife's fidelity on the one hand, and of persecution, surveillance, and poisoning by anonymous enemies on the other. The two authors, who describe themselves as " verbally fluent people who normally enjoyed a rational and friendly argument ", had 16 joint discussions with the patient of about an hour's duration each (4 per week for 4 weeks) during which they attempted to demonstrate to him the palpable falseness of his delusions. The patient was at first hostile, but soon became cooperative and glad to talk. He was also asked to answer 4 questionaries (reproduced in detail) at each interview by placing the question cards in 5 appropriate heaps, this being done on 8 occasions before the interview and on 8 after it. The questionaries were designed to reveal depression, hostility, guilt, and paranoid beliefs respectively, but only the last two categories proved to be of value. Each answer was scored on a five-point scale ranging from " this is definitely the case " to " this is definitely not the case ".

It was found that there was no difference between the individual effects exercised by the two interviewers and that there was no immediate change in the strength of the patient's delusions after interviews. Thus in the course of the 16 interviews the patient remained unshakably convinced of his guilt and unworthiness. But the strength of his paranoid beliefs was reduced at least from " this is definitely the case " to " this may be the case "; also he had been " not sure " of his wife's infidelity at the beginning of the experiment and became convinced that " this is definitely not the case " at the end. He also became convinced that it was not true that his enemies tried to poison him. Quantitative evaluations showed that the reduction of the strength of paranoid beliefs was statistically significant. But most of the change in strength occurred during weekends when there were no interviews.

The patient was discharged " much improved " 3 months after the last interview. The authors remark that the reduced strength of the patient's paranoid beliefs could have been incidental, or a sign of clinical improvement unrelated to the discussions. [They do not emphasize the fact that only a few of the patient's paranoid beliefs reached delusional strength, whereas this was the case with his feelings of guilt and unworthiness, which also remained impervious to rational discussion.] *F. K. Taylor*

204. **The Effects of Chlorpromazine upon Psychomotor and Psychiatric Behavior of Chronic Schizophrenic Patients**
F. HEILIZER. *Journal of Nervous and Mental Disease* [*J. nerv. ment. Dis.*] **128**, 358–364, April [received July], 1959. 8 refs.

The author, working at the Veterans Administration Hospital, Canandaigua, New York, has examined the effects of chlorpromazine on a group of 64 male patients with chronic schizophrenia. The tests used were: measures of fine movements (reaction time and finger dexterity), which seem to be especially sensitive to the schizophrenic process; the Lorr Interview Scale to measure more restricted areas of behaviour and general morbidity; and the Bender–Gestalt test as a measure of perceptual-motor performance. Changes in the patients' weight during the period of the trial were also noted. The patients were divided at random into two [presumably equal] groups, one of which received 300 mg. of chlorpromazine a day and the other a placebo for a period of 3 months. The interview was given before and again 12 weeks after the start of this period, scores being obtained on both occasions from 48 patients. The other tests were applied before and again 2 and 8 weeks after the start of treatment, 44 patients completing them. Half of the subjects completing each test were in the chlorpromazine group and half in the placebo group; those administering the tests were not aware of the nature of any patient's medication. At the end of the 3 months all the patients received the placebo for 6 weeks and were then retested.

From the results of the tests 14 measures of morbidity were obtained for each group and the mean values were subjected to analyses of variance. These indicated that the group treated with chlorpromazine differed signifi-

cantly ($P<0.05$) from the control group in three respects —decreased variability in reaction time (but only in those subjects with a high initial score), increased depression in the A factor of the Lorr Scale (ratings for affect, mood swings, and level and amount of speech), and decreased perceptual distortion in the F factor of the same scale (ratings for hallucinations, delusions, hostility, and orientation for people). There was no significant difference in respect of the general morbidity measure (the total score for the Lorr Interview Scale), indicating that chlorpromazine did not produce a general effect on behaviour, but acted more selectively. Rank order correlations were then computed among all the variables (including measurements of weight) showing significant differences. Significant correlations were found between variability in reaction time, body weight, and the A factor on the Lorr Scale. Alterations in the F factor were not part of this general matrix of change. Measurements of the effects of the drug by means of the A factor were discrepant in that chlorpromazine reduced the level of alertness for the group as a whole, whereas a positive relationship was found between increased alertness, the more consistent reaction time, and gain in weight. It is concluded from this that chlorpromazine in high dosage interferes with improvement of this matrix of behaviour and that the therapeutic practice of giving increasing doses in the absence of marked behavioural changes needs to be more carefully assessed.

None of the tests of fine movement, included because of their reputed sensitivity to the schizophrenic process, yielded significant information concerning the effects of the drug. The results of an attempt to evaluate the effect of the drug in terms of the patients' behaviour before the trial were inconclusive, as also were those of analysis of the results of retesting after the final 6-week placebo period. *F. E. Kenyon*

TREATMENT

205. **Chemical Shock Therapy with 7843 R.P.** (Le chimio-choc au 7843 R.P.)

R. COIRAULT, V. GIRARD, R. JARRET, and J. ROUIF. *Annales médico-psychologiques* [*Ann. méd.-psychol.*] **2**, 45–72, June, 1959. 3 figs.

The authors report from Val-de-Grâce Hospital, Paris, extensive observations on the therapeutic effects of a chlorpromazine derivative, 7843 R.P. (dimethylsulphamido-3-(N-methylpiperazinilpropyl)-10-phenothiazine) in psychotic and neurotic conditions. An elaborate hypothesis concerning its action in relation to that of electric shock treatment is discussed. In contrast to chlorpromazine, 7843 R.P. has little hypotensive effect and is a feeble adrenaline antagonist, has no antihistamine effect, and is only slightly hypothermic. Its anti-emetic action is 40 times greater than that of prochlorperazine and it has characteristic motor effects. Its toxicity is low. Administration is preferably discontinuous, the drug being given on 5 successive days and the course repeated only after the motor symptoms have subsided or for 2 days at a time followed by 2 or 3 days' rest. In treating 30 patients the authors began with a dosage of 20 mg. a day, given intramuscularly, increasing it until motor effects were produced—up to 60 mg. a day being required. The motor syndrome produced by 7843 R.P. was rarely an akinetic and more frequently a hyperkinetic state, including opisthotonus, torticollis, and sucking movements. Increased salivation often leading to difficulties of respiration and deglutition occurred. There was sinus tachycardia and the blood pressure occasionally rose slightly, but more often fell. Sweating and thirst developed. It was sometimes necessary to arrest the motor crisis by means of chlorpromazine, " phenergan " (promethazine hydrochloride), or other drugs.

The patients treated were suffering from acute delusional states (7), schizophrenic states (7), agitation (2), and neurotic states (14). In the first group success was dramatic. The motor symptoms captured the whole attention of the patient and, with additional suggestion by the physician, eventually seemed to replace the psychiatric symptoms, leaving him more in contact with the outside world. All of the schizophrenic patients showed dissociative phenomena initially. After treatment the paranoid ideas of one patient disappeared, 2 with simple schizophrenia resumed family life, one hebephrenic was allocated skilled work in the hospital, and 2 patients with a chronic hallucinatory state were improved. The motor phenomena in these patients evoked symptoms of pathological anxiety. The 2 agitated patients, who had not been helped by chlorpromazine, were improved without the advent of motor phenomena. Among the neurotic patients were included cases of anxiety state, phobias, obsessional states, neurotic depression, and pre-psychotic states. In such cases 7843 R.P. seems to produce a " biological facilitation " which, together with psychotherapy, arrests the process of dissociation. Its action is symptomatic, extending only to the immediate situation and not to deeper causes. The mode of action appeared to be partly similar to that of the neuroleptic drugs, but partly also through its motor effects, which appeared to focus the patient's attention. The anxiety stimulated was also thought to be beneficial. The aggressivity in some patients had a cathartic effect. There was no clear relationship between the disorder and the type of motor effect produced by the drug. The amount of psychotherapy could not be reduced, the presence of a physician being essential.

From daily studies of neuromuscular activity oscillating curves were recorded, corresponding to the drug's daily influence upon metabolism and cell-membrane potential. Hyper-excitability was followed by hypo-excitability when small doses were given. The lowering of excitability corresponded to increased urinary output of calcium. The changes persisted for some time after the treatment was stopped. The serum calcium level was increased and also, to a lesser extent, that of magnesium, while the potassium level fell; the effect on the sodium level was variable. Urinary excretion of calcium and magnesium was increased as also was that of potassium. Variable changes in the blood sugar level were noted, including both hyper- and hypo-glycaemia. Administration of glucose prolonged the symptoms, whereas insulin intensified them. *J. S. Bearcroft*

206. **Deaths Associated with Electroplexy**
J. C. BARKER and A. A. BAKER. *Journal of Mental Science* [*J. ment. Sci.*] **105**, 339–348, April [received July], 1959. 20 refs.

Information concerning the frequency and causes of death associated with electric convulsion therapy (E.C.T.), with special reference to the different techniques used, was obtained by sending questionaries to 13 teaching hospitals in London and to 42 mental hospitals. The number of individual treatments given varied from 100 to 8,000 per annum at different hospitals, the total for the 2 years 1956 and 1957 being 259,000. During this period 9 deaths occurred within 3 days of the last treatment, an incidence of 0·0036%. This figure is lower than those previously recorded in the literature.

Of the 9 fatalities, 8 occurred in patients over 60 years of age, 6 of whom had evidence of pre-existing physical disease. All 9 patients had had more than one treatment before death—a finding which is at variance with that of Mackay (*Proc. roy. Soc. Med.*, 1953, **46**, 13; *Abstr. Wld Med.*, 1953, **14**, 75), who found that almost half of 329 deaths associated with E.C.T. followed the first convulsion. Four patients in the present series were receiving tranquillizing drugs at the time of death, and all of these died of shock or cardiac failure shortly after treatment. In 7 of the 9 cases death followed modified E.C.T., but this is held to reflect the popularity of modified procedures rather than an increase of risk associated with them. There were 2 deaths from coronary thrombosis and one from cerebral haemorrhage, the remainder, which occurred suddenly or shortly after treatment, being usually attributed to acute cardiac failure or shock. Necropsy findings in these last cases were notably meagre. No evidence was found to show that any particular technique of E.C.T. carried less risk to life than others. *J. S. Bearcroft*

207. **Prolonged Apnoea following E.C.T. Modified by Suxethonium (Brevidil " E ")**
J. C. BARKER and A. MAY. *Journal of Mental Science* [*J. ment. Sci.*] **105**, 496–503, April [received July], 1959. 42 refs.

Prolonged apnoea following suxethonium (" brevidil E "), a short-acting muscle relaxant used for modifying electrically induced convulsions, does not appear to have been reported previously, though numerous examples of this complication have been described following suxamethonium (succinylcholine, " scoline "), a closely related chemical compound. Three cases of prolonged apnoea following suxethonium (1 hour, 45 minutes and 10 minutes) are described, all of whom showed low serum pseudocholinesterase levels. The causes of this complication are discussed in the light of this finding, together with the mode of action of the depolarizing group of relaxants to which suxethonium belongs. Other factors must be responsible for prolonged apnoea when the pseudocholinesterase levels are normal, and these are discussed.

The importance of apnoea following modified E.C.T. [electric convulsion therapy] is stressed, since it has been ascertained that at approximately 85% of hospitals that give E.C.T. muscle relaxants are used. Suxethonium is used at 22%. However, consultant anaesthetists are present at only 50% of mental hospitals during routine electroplexy sessions. Some points concerning methods of prevention and treatment of prolonged apnoea are given.

It has been suggested that PAM (pyridine-2-aldoxine methiodide) which successfully reverses some of the symptoms of alkyl-phosphate (parathion) poisoning, and restores the serum pseudocholinesterase to normal levels, might act as a specific antidote in these cases of prolonged apnoea, and it is intended to try out this preparation in the future.—[Authors' summary.]

208. **Modification of the Circulatory Response to Electroshock Therapy by Thiopental**
L. D. EGBERT, P. A. DUMAS, G. C. GINTER, and J. E. ECKENHOFF. *Anesthesiology* [*Anesthesiology*] **20**, 309–312, May–June, 1959. 19 refs.

Electric convulsion therapy (E.C.T.) profoundly affects the circulation for a short period. Of one reported series of 33 deaths following E.C.T., 10 were due to circulatory failure. Since barbiturates may modify the circulatory response the authors studied the effect of intravenous administration of thiopentone and succinylcholine (suxamethonium) one minute before the shock in 8 patients at the Hospital of the University of Pennsylvania, Philadelphia. Two dose levels of thiopentone were used—100 mg. and 500 mg. A dose of 500 mg. considerably modified the rise in blood pressure and lessened the duration of the hypertension. Tachycardia was also reduced. The duration of apnoea and of sleep after treatment was significantly longer with the larger dose than with the 100-mg. dose of thiopentone.

The authors consider that thiopentone should be useful in modifying the circulatory response in patients with cardiovascular disease undergoing E.C.T., and that it acts by interfering with the central sympathetic outflow.
W. Stanley Sykes

209. **Effects of Iproniazid in Depressive Syndromes**
E. D. WEST and P. J. DALLY. *British Medical Journal* [*Brit. med. J.*] **1**, 1491–1494, June 13, 1959. 12 refs.

Iproniazid (" marsilid ") has been reported to be effective in the treatment of depressive states in 25 to 75% of cases, but whereas some workers regard it as invaluable, others consider it too dangerous for clinical use owing to its toxic effect on the liver. The present authors conclude from their experience at St. Thomas's Hospital, London, in the treatment of 500 cases that there is a type of case, recognizable from the history, which is more likely than others to benefit from the drug. They give details of the response of 101 patients to iproniazid, of whom 58 improved to a notable degree. These were mostly cases of somewhat " atypical " depressive states, sometimes resembling anxiety hysteria with secondary depression. A number of patients improved with iproniazid after other treatments had failed, while in other cases a great reduction in frequency of electric convulsion therapy (E.C.T.) became possible —for example, a woman of 83 who had had 170 induced

convulsions was able to do without E.C.T. when taking 25 mg. of iproniazid daily.

The initial dosage was 50 mg. 3 times a day for 2 weeks, the patient being warned to stop taking the drug if he felt ill and to reduce the dose if dizziness was troublesome. After 2 weeks the dosage was progressively reduced to the lowest effective level, which in some cases was as little as 25 mg. a day. Constipation, paraesthesiae, muscle twitching, and (in the elderly) hypotension were also noted. Lethargy was combated with dexamphetamine. A sudden gain in weight and the development of oedema or jaundice were indications for the immediate cessation of treatment. An incidence of such complications of 1 in 2,000 or possibly more has been reported in other series, with a mortality of 20%. The authors themselves have seen only one case of jaundice, with recovery, among 500 treated. The tendency of iproniazid to cause a facial flush prevented the trial from being "blind", but analysis of the symptoms before treatment in the 58 patients who improved and in the 43 who did not shows a striking difference between the two groups. [This analysis should be consulted in the original paper by those selecting cases for treatment with iproniazid.] An interesting point is that 78% of the patients who were improved (and only 42% of those who were not) had cardiovascular symptoms. In one case of well-developed Raynaud's disease with a family history the patient was free from attacks while taking 50 mg. of iproniazid twice a day, but became subject to them again when the drug was withheld.

In some of the more typical cases of endogenous depression iproniazid was more effective than any other treatment had been in preventing the return of cyclical depression. Such patients were kept on a minimum dosage and told to increase it when they felt the depression returning—with success in 10 out of 12 cases.

K. W. Todd

210. **Tranquillizers, a Latin Square Trial**
M. J. CRAFT. *Journal of Mental Science* [*J. ment. Sci.*] 105, 482–488, April [received July], 1959. 12 refs.

In an investigation carried out at Balderton Hospital, Nottinghamshire, the author attempted to assess the value of certain drugs in reducing hyperactivity in mental defectives. A total of 18 patients, aged 15 to 44 years, were selected for the trial because of outstanding hyperactivity, aggression, and bad social habits. All the patients had an I.Q. below 34. The trial lasted for 165 days; a preliminary period of 39 days was followed by 6 equal periods of 3 weeks, during each of which one of the following drugs was given: amylobarbitone, amphetamine, promethazine, acetylpromazine, promazine hydrochloride, and prochlorperazine. During the first week of the period the dosage of each drug was progressively increased and during the third week it was progressively decreased. During the second week the daily dosages were: amylobarbitone 6 gr. (0·4 g.), amphetamine sulphate 30 mg.; promethazine hydrochloride 150 mg.; acetylpromazine 150 mg.; promazine hydrochloride 600 mg. (except in 2 instances in which 300 mg. was given); and prochlorperazine 150 mg. The design of the trial ensured that each patient received each drug during one 3-week period, that during any period all 6 patients in any group received a different drug, and that "each drug was followed by every other drug once only in each group".

Behaviour was recorded by nurses (who did not know the nature of the treatment) according to: (1) activity, graded from destruction of any article (+6) through normal (0) to stuporose (−6); (2) aggression, ranging from injury to others (+6) to injury to self (−6); and (3) social behaviour, from spitting and shouting (+6) to eating excreta (−6).

Analysis revealed that in respect of aggression there was no apparent difference between the drugs, although there was a steady increase in aggression throughout the 165 days. The author suggests this was possibly due to a cumulative effect of the drugs, or to the effect of confinement of the patients indoors, or to a steady change in the standards of judgement of the nurses. All the drugs had a "similar small effect" in reducing activity, amylobarbitone and promazine being the least effective. Amphetamine, promethazine, acetylpromazine, and prochlorperazine were found to have a definite residual effect after administration ceased. No significant changes in social behaviour were observed with any of the drugs.

In 6 patients undue sedation with staggering gait was observed with promazine, acetylpromazine, promethazine, and prochlorperazine. Hypotensive episodes occurred in 2 patients given promazine hydrochloride and in 2 given acetylpromazine. In 4 patients taking prochlorperazine signs of Parkinsonism developed.

G. de M. Rudolf

211. **The Value of Leucotomy in Relation to Diagnosis**
A. A. ROBIN. *Journal of Neurology, Neurosurgery and Psychiatry* [*J. Neurol. Neurosurg. Psychiat.*] **22**, 132–136, May, 1959. 2 figs., 1 ref.

At Runwell Hospital, Wickford, Essex, the author has attempted to evaluate the effect of leucotomy in schizophrenia, affective disorders, paraphrenia, and epilepsy by comparing the results obtained with those in patients suffering from similar disorders but not subjected to leucotomy. Of 188 patients with schizophrenia, 91 had been operated on and 97 had not, the two groups being comparable as regards sex and age distribution and duration of stay in hospital. The discharge rate was higher in the group subjected to leucotomy than in the controls, but this improvement was temporary, the number of readmissions being higher than in the controls; the long-term results were comparable in the two groups. A total of 52 patients with affective disorders (manic-depressive psychosis, mania, or depression) had been operated on, and the results were compared with those in 48 similar patients not so treated. There was no difference attributable to leucotomy between the two groups, nor was there any difference between the results obtained in patients suffering from paraphrenia and epilepsy who were operated on and a control group of similar patients.

The author states that in patients who recovered, whether operated on or not, the results were comparable when sufficient numbers became available for comparison.

E. H. Johnson

Paediatrics

NEONATAL DISORDERS AND PREMATURITY

212. **Use of a Nasal Antibiotic Cream during a Nursery Outbreak of Staphylococcal Disease**
J. O. KLEIN and E. F. H. ROGERS. *New England Journal of Medicine* [*New Engl. J. Med.*] **260**, 1012–1015, May 14, 1959. 1 fig., 3 refs.

Outbreaks of staphylococcal infection among newborn infants in nurseries are not infrequent, but may not always be apparent to the hospital staff at the time because of the long incubation period, so that many staphylococcal skin lesions first appear in these infants after discharge from hospital. Thus it was noted in central New York by public health nurses that out of 59 infants born over a 2-month period in one hospital, 19 developed skin lesions after discharge to home; the hospital personnel were unaware that this problem existed.

In this study undertaken by the New York State Department of Health cultures of nasal secretions from 22 nurses and 8 doctors concerned showed that 10 were harbouring coagulase-positive staphylococci. These subjects were treated with antibiotics and all subsequent cultures were negative. The closure of the nursery, a review of the aseptic technique employed, and the opening of a new nursery resulted in only a temporary reduction in the proportion of children with skin lesions, although only one nurse was then carrying staphylococci in the nose. Infants and nurses were then treated with nasal cream containing "2·5 mg. of neomycin and 0·25 mg. of gramicidin in a bland base" for 1 week. In the 6 months preceding this trial [winter months] 29% of the infants who were followed up had skin lesions, but in the 4 months [summer] following the trial none had skin lesions. It is believed that infant-to-infant transmission is the main source of spread of the organism.

[There were no concurrent controls, and the difference in the seasons might have been a factor which is not considered by the authors.] *John Lorber*

213. **Physiological Jaundice**
A. A. CUNNINGHAM. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **34**, 262–268, June, 1959. 3 figs., 5 refs.

The author studied the incidence of "physiological jaundice" in a consecutive series of 1,000 infants born in the maternity unit of Kingston Hospital, Surrey. Infants weighing 2½ lb. (1·1 kg.) or less at birth, those with haemolytic disease of the newborn, and a few who died before jaundice could develop were not included. The methods of bilirubin assay used—namely, the Daly "macro" and the "micro" methods—are described in detail.

In 14% of the infants the maximum serum bilirubin concentration was over 5 mg. per 100 ml. and in 3·4% it was over 10 mg. per 100 ml. The incidence of jaundice was highest in the group of 63 premature infants, in 11 of whom the maximum serum bilirubin level was above 15 mg. per 100 ml. The author states that in about 10% of premature infants there is some risk of kernicterus developing. In the present series none of the infants weighing over 5½ lb. (2·5 kg.) at birth developed a serum bilirubin concentration of 15 mg. per 100 ml. and only 2% had a maximum concentration of 10 mg. per 100 ml. or more. There was no evidence that ABO haemolytic disease was a causative factor in the development of jaundice.

In a second series of 119 infants, 39 of whom had clinical jaundice, no correlation was found between subsequent development of jaundice and the bilirubin level in cord blood, except that in the infants without jaundice the level was 2·5 mg. per 100 ml. or less, whereas it was over this figure in 13 of the 39 infants who became jaundiced; even in these, however, it was rarely above 3 mg. per 100 ml. *E. H. Johnson*

214. **Changes in Heart Size in the Dyspnoeic Newborn Baby**
E. D. BURNARD. *British Medical Journal* [*Brit. med. J.*] **1**, 1495–1500, June 13, 1959. 8 figs., 45 refs.

The heart was larger in the radiographs of premature babies suffering dyspnoea than in similar babies without dyspnoea. The heart size diminished as the symptoms improved. In mature babies suffering dyspnoea the heart size was greater than in normal babies cited from the literature. The association for a greater or less time of the crescendo systolic murmur with cardiac enlargement was noted. The association between murmur and dyspnoea had been shown previously.

The triad of murmur, dyspnoea, and enlargement occurred in full-term babies after birth asphyxia and in premature babies whether they had been asphyxiated at birth or not. Both enlargement and the murmur were early phenomena in babies with dyspnoea. This association, coupled with the apparent paradox of a slow heart rate in the presence of severe dyspnoea, and related to evidence of a limited ability in the newborn to increase cardiac output, led to the suggestion that cardiac insufficiency was present from an early stage.

Necropsy findings in the lung could be interpreted on the basis of vascular congestion. The early radiological appearances could mean that congestion and oedema were developing. The suggestion was therefore made that insufficiency on the left side of the heart was the cause of pulmonary congestion and the subsequent symptoms. Asphyxia during birth brought this about in the full-term baby. In the premature child born without asphyxia a defective respiratory mechanism had to be presupposed.

The implications of these views for management were mentioned.—[Author's summary.]

215. **Intestinal Obstruction in the Neonatal Period Due to Agenesis of the Myenteric Plexus**
A. I. CHENOWETH. *Annals of Surgery* [*Ann. Surg.*] **149**, 799–806, June, 1959. 4 figs., 16 refs.

Congenital megacolon (Hirschsprung's disease) in the older infant and in the child is now readily recognized, clearly understood and, in the main, satisfactorily managed. When, however, it presents in the neonatal period as acute intestinal obstruction it is very often fatal, survival depending on correct management. At the Children's Hospital, Birmingham, Alabama, the author has seen 4 cases (3 being fatal) in which the agenesis of the myenteric plexus was in the distal colon and one fatal case in which the agenesis was in the terminal ileum. When admitted to hospital the infants had typical neonatal intestinal obstruction which had failed to respond to conservative measures; laparotomy was performed in all 5 cases.

The author emphasizes the importance of correct siting of the enterostomy, intestinal biopsy being carried out to achieve this where facilities are available. When the agenesis is distal a transverse colostomy is essential; when it is in the terminal ileum an ileostomy may be life-saving. Agenesis of the plexus of the terminal ileum is usually confined to the distal 3 cm., which is narrow and full of impacted faeces, and the distal colon is collapsed as in small bowel atresia. Differentiation from meconium ileus may be difficult.

(A contributor to the discussion of this paper emphasized the high mortality associated with Hirschsprung's disease when it becomes manifest in early infancy; he advocated a transverse colostomy so as to be reasonably sure of being above the aganglionic segment.)

[The treatment advocated includes nothing that is not current practice in Great Britain and the mortality in this very small series is perhaps exceptionally high. However, the paper serves a useful purpose in drawing attention to an important cause of acute intestinal obstruction in the newborn infant.]

Andrew M. Desmond

216. **A Longitudinal Study of the Growth and Development of Prematurely and Maturely Born Children. Part IV. Morbidity**
C. M. DRILLIEN. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **34**, 210–217, June, 1959. 6 figs., 9 refs.

In this further contribution to a series of studies of growth and development in premature infants carried out in the Department of Child Life and Health, Edinburgh, the health history of nearly 600 prematurely born and full-term children in the first 2 years of life is analysed. The children were visited at 6-monthly intervals and a history taken of any illness necessitating medical attention or hospital admission. The findings may be summarized as follows. Premature children suffered from more illness in the first year of life than children born at term. More than 85% of all illness requiring medical attention was infective in origin, nearly one-half being due to respiratory infections. The incidence and severity of respiratory infection were highly correlated with the standard of maternal care. Premature children were affected to a greater extent by adverse environment than full-term children from similar homes. The incidence and severity of gastro-intestinal infections, measles, and whooping-cough were also highly correlated with the standard of maternal care. As expected, there was a much higher incidence of septic skin infection when the mother's care was unsatisfactory. It is of interest that infantile eczema occurred predominantly in intelligent children of good mothers. As regards congenital defects it was found that the lower the birth weight, the higher was the incidence of such defects.

R. S. Illingworth

CLINICAL PAEDIATRICS

217. **A Practical Method for the Measurement of Systolic Blood Pressures of Infants**
H. V. RICE and L. J. POSENER. *Pediatrics* [*Pediatrics*] **23**, 854–860, May, 1959. 4 figs., 6 refs.

Since assessment of the blood pressure in infants by standard methods is often difficult and the results may be unreliable, a new method of measuring the systolic blood pressure in infants has been tried in the Department of Pediatrics, St. Paul's Hospital, Vancouver. An occlusive cuff and pressure gauge, similar to that of a standard sphygmomanometer, surround the upper arm and a pulse pressure indicator connected to an optical system surrounds the limb distal to the occlusive cuff. The occlusive cuff is slowly inflated to a pressure which is a few millimetres higher than that required to occlude the arteries and this pressure is then slowly reduced until deflections of the light beam reappear.

The results obtained with this method were compared with those obtained by palpation and auscultation in 10 patients and by the flush technique in 68, all of whom were under the age of one year. A slightly higher blood-pressure reading was obtained by this new method [but its final accuracy must await further investigation]. The authors state that it is not yet possible to determine the diastolic pressure by this method, and the systolic pressure readings are unreliable in restless infants.

R. M. Todd

218. **Chronic Ulcerative Colitis in Childhood: a Follow-up Study**
R. C. KING, A. E. LINDNER, and H. M. POLLARD. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **34**, 257–261, June, 1959. 24 refs.

A follow-up study is reported of 52 cases of chronic ulcerative colitis in childhood seen at University Hospital, Ann Arbor, Michigan, between July, 1947, and June, 1956. At onset of symptoms the patients were 5 to 15 years of age, and in all cases the diagnosis was confirmed by sigmoidoscopy and x-ray examination. The commonest radiological finding was loss of normal haustral markings, and this involved the entire colon in 30 cases. Sigmoidoscopy revealed a definite abnormality in 46 cases.

Of the 51 patients for whom follow-up information was complete, 9 had died and 4 (duration of the disease

9 years or more) had carcinoma of the colon. Excision had been carried out in 11 cases, with one death. Of the 10 survivors, 9 described their condition as excellent, whereas only 17 of the 31 patients treated medically did so; in 14 of the latter group the disease continued to be active.

The authors consider that better results than those revealed by this study might be achieved if surgical treatment were more frequently carried out in ulcerative colitis in childhood. *E. H. Johnson*

219. **Changes in Gastric Secretion in the Treatment of Dystrophic Infants with Gastric Juice.** (Изменение желудочной секреции под влиянием лечения натуральным желудочным соком у детей раннего возраста при дистрофии)
G. E. Ryžova. *Педиатрия* [*Pediatrija*] **37**, 60–63, June, 1959. 23 refs.

In infantile dystrophy the function of the gastro-intestinal tract is disturbed, there being lowering of gastric acidity and diminished enzyme content of the stomach. Numerous experiments have confirmed the stimulating effect of natural gastric juice on the secretion of the stomach and pancreas. In this study reported from Lvov 31 children, aged from 2 months to 2 years, with dystrophy of the second degree were investigated before and during treatment with gastric juice. Gastric analyses for acid and pepsin secretion, as well as estimation of the rate of emptying of the stomach, were performed. Natural gastric juice was then administered in a dosage of one teaspoonful three times a day 15 minutes before food and the above investigations repeated at intervals during the treatment, which lasted for various periods ranging from 8 to 78 days.

Before treatment free hydrochloric acid was absent from the fasting juice in 11 cases and in the remainder varied in volume from 3 to 12 ml. After a test meal 10 of these children still showed no free acid, and the average for the group was 2·6 ml. After treatment the general condition of the infants greatly improved, and they gained from 80 to 1,510 g. per month (average 377·4 g.). The volume of gastric juice secreted per hour and total acidity increased in all cases, while the free acid level and pepsin content increased in 20 of the 31 children. A further 7 patients shared in the general improvement and gain in weight without, however, any increase in the gastric secretion, while 4 children, suffering from chronic dysentery showed no improvement. *L. Firman-Edwards*

220. **Air-cysts of Small and Large Intestine in Infancy.** (Воздушные кисты тонкой и толстой кишки у детей грудного возраста)
M. L. Zolotavina and V. A. Karmilova. *Педиатрия* [*Pediatrija*] **37**, 73–76, May, 1959. 1 fig., 9 refs.

The authors describe 2 cases of multiple air cysts (pneumatosis) of the intestine in infants. Both cases were fatal, and in one pulmonary air cysts, not communicating with the bronchi, were also found at necropsy. Clinically the children had suffered from loss of weight from birth, lack of appetite, regurgitation of food, liquid stools, subfebrile temperature, and abdominal distension. In one case the erythrocyte sedimentation rate was 30 mm. but in the other it was only 3 mm. in one hour; leucocytosis was present in both cases. In one case *Proteus morganii* was isolated from the stools, but in the other no pathogen was found.

On the basis of only 2 cases the authors do not venture to suggest the cause of onset of the pneumatosis, but are inclined to the view of Kobrizhko that in this condition the primary cause is maldevelopment of the intestinal lymphatic vessels. If such an abnormality were present the invasion of the intestinal walls by gas-forming bacteria could result in the formation of air-cysts. Avitaminosis may also play a part. The attention of paediatricians is called to the need for establishing criteria for the early diagnosis of pneumatosis, since immediate operative treatment might be life-saving.
L. Firman-Edwards

221. **Changes in the Pancreas in Certain Diseases of Children.** (Изменения поджелудочной железы при некоторых заболеваниях у детей)
N. V. Orlova. *Педиатрия* [*Pediatrija*] **37**, 68–73, May, 1959. 12 refs.

The changes in pancreatic function in respect of both the external and internal secretions of this gland were studied in 25 children suffering from pneumonia and 31 with acute rheumatism. The production of insulin was estimated by plotting blood sugar curves over a period of 3 hours after a loading dose of glucose, and the digestive secretory function by estimating the blood diastase level before and after sugar loading, and also by determining the urinary diastase excretion.

In only one-third of the cases of pneumonia, and these the patients with the mildest and most localized disease, were the glucosé curve and the blood diastase level normal. In the remaining two-thirds one of four abnormal types of reaction was found. In one-half of the cases the urinary excretion of diastase was 2 to 10 times the normal maximum level. In about half the cases the abnormal findings did not return to normal with the disappearance of clinical symptoms, this being especially noticeable in those in which chronic pneumonitis had developed. Of 17 children with a first attack of rheumatism the blood sugar curve was normal in only 5, while it was abnormal in all 14 with recurrent attacks, departing farthest from the normal in patients with the exudative type of rheumatism. The urinary excretion of diastase was normal in only one-third of all cases. At the end of one month half the children still showed abnormal blood sugar curves, and after 2 months one-third continued to do so. The urinary excretion of diastase, which had been raised at first, fell to normal on clinical recovery, but rose again with exacerbations of the disease.

In addition to these studies *in vivo* histological examination was also carried out of the pancreatic tissues of 30 children dying of pneumonia and 2 of rheumatism, but no important changes were found. The evidence points to the conclusion that most of these changes in pancreatic function are basically of a functional character.
L. Firman-Edwards

Public Health and Industrial Medicine

222. **The Mortality from Arteriosclerotic and Hypertensive Heart Diseases in the United States. II. Possible Relation to Industry**

L. H. SIGLER. *American Journal of Cardiology* [*Amer. J. Cardiol.*] **3**, 605–610, May, 1959. 8 refs.

In a previous paper (*Amer. J. Cardiol.*, 1958, **1**, 176; *Abstr. Wld Med.*, 1958, **24**, 227) the author showed that mortality from arteriosclerotic and hypertensive heart diseases varied markedly in different parts of the United States. In the present paper he reports a study of the concentration of industry in relation to mortality from these diseases, the different States being classified into groups according to density of major manufacturing establishments, from Group I (less than 5 sq. miles 12·95 sq. km.) per factory) to Group V (more than 100 sq. miles (259 sq. km.) per factory).

There was a general correlation between mortality from arteriosclerotic heart disease and industrial concentration, the crude death rate (per 100,000 population) averaging 257·7 in Group I and falling progressively to an average of 156·1 in Group V. Although the association was also apparent within each group, there were occasional exceptions—for example, North and South Carolina, Georgia, West Virginia, and Tennessee had relatively low mortality rates despite heavy industrialization, while the converse was true in South Dakota and Montana. A similar but less marked parallelism was observed between the death rates from hypertensive heart disease and industrial concentration. The average mortality rates for Groups I and V were 68·9 and 31·0 respectively, but there was little difference between Groups II, III, and IV, in which the average death rates were respectively 54, 59·8, and 52·2 per 100,000.

It is suggested that the observed trend is likely to be due to a multiplicity of factors, including air pollution, the effect of tobacco, and psychological stress; in the author's view, differences in dietary habits are probably unimportant. [The possible influence of physical activity is not mentioned.] *S. G. Owen*

223. **Studies in the Epidemiology of Tinea Pedis. I. Tinea Pedis in School Children**

M. P. ENGLISH and M. D. GIBSON. *British Medical Journal* [*Brit. med. J.*] **1**, 1442–1446, June 6, 1959. 2 figs., 14 refs.

In this study of the epidemiology of tinea pedis, which was carried out in Bristol during the winter and spring of 1956–7, approximately 4,800 children aged 7 to 14 years attending 6 secondary modern boys' schools, 6 secondary modern girls' schools, and 4 junior boys' schools were examined. Teachers were asked to select about 80 children from each year with no attempt at statistically random sampling; usually this method produced a whole class at a time. The schools selected for study were those using three corporation swimming baths in widely separated parts of Bristol. Clinical, microscopical, and cultural examinations for tinea pedis were made. In all, 1,839 boys and 2,061 girls aged 11 to 14 from the 12 secondary modern schools and 894 boys aged 7 to 10 years from the 4 junior schools were examined.

Of the senior boys, 40·3% had lesions of the feet (excluding plantar warts and blisters) and 6·6% had tinea pedis; of the senior girls, 30·4% had lesions and 1·6% had tinea pedis, while of the junior boys, 33·2% had lesions and 2·2% had tinea pedis. Of the 179 infections found, 84·4% were due to *Trichophyton mentagrophytes*, 7·2% to *T. rubrum*, and 3·9% to *Epidermophyton floccosum*; 4·4% of the infections were identified by microscopical examination only. No correlation was found between the infection rate and cleanliness, the presence of non-mycotic lesions, social class, or the use of school shower-baths, but there was a high correlation between infections in boys' schools and the district in which the schools were situated. The authors conclude that the local swimming bath and the frequency with which it is used are important factors in fungal infection of the feet in school-children. *R. R. Willcox*

224. **Studies in the Epidemiology of Tinea Pedis. II. Dermatophytes on the Floors of Swimming-baths**

M. P. ENGLISH and M. D. GIBSON. *British Medical Journal* [*Brit. med. J.*] **1**, 1446–1448, June 6, 1959. 5 refs.

In view of the conclusions reached in the investigation into the epidemiology of tinea pedis described above [see Abstract 223] the three swimming baths in Bristol used by the children were investigated by means of velvet-covered sampling pads which were then pressed on to a glucose–peptone–agar medium with added antibiotics, as in the method described by Gentles (*J. clin. Path.*, 1956, **9**, 374). Samples were taken from the sides of the pools and also from the floors of changing cubicles, shower-baths, lavatories, passages, and wooden slats. Of 67 pads so exposed in the three swimming baths after 7 to 8 hours' use, 12 were found to be infected (40 colonies). The fungus was found more often in the bath used by children from a district with a high incidence of tinea pedis than in the other two baths which were used by populations with a lower incidence. The baths were cleaned twice daily with brooms and a solution of "chloros". Tests after sluicing with water, when only 1 of 21 pads was found to be contaminated, indicated that the cleansing method employed was adequate if conscientiously carried out; it is notable that the two least contaminated baths were frequently sluiced down with buckets of water at intervals during the day, whereas in the case of the most contaminated bath no such treatment was given.

Examinations were also made of the swimming-bath staff. These showed that the feet of 8 of 14 atten-

dants whose duties entailed entering the water were infected, whereas tinea pedis was found in none of the 11 persons who never had to enter the water.

R. R. Willcox

225. **Relationship of Type of Vaccine and Method of Inoculation to Vaccination Reactions after Immunization against Whooping Cough, Diphtheria, and Tetanus.** (Het verband tussen de aard van de gebruikte entstof, de wijze van inspuiten en de ent-reacties na immunisatie tegen kinkhoest, difterie en tetanus)
A. TASMAN. *Nederlands tijdschrift voor geneeskunde* [*Ned. T. Geneesk.*] **103**, 1049–1057, May 16, 1959. 4 figs., 5 refs.

The reactions were studied 1, 3, and 8 days and 1 and 2 months after vaccination in 338 children who were given mixed diphtheria and tetanus toxoid and pertussis vaccine and in 94 children who were given diphtheria and tetanus toxoid only. The children were aged 6 years or less, and the sexes about equal.

In 275 cases a single inoculation was given and in the remainder 2 or 3 at a month's interval. The reactions observed were mostly local and were more frequent and more severe and lasted longer after subcutaneous than intramuscular injection. Preparations containing pertussis antigen gave more reactions than those without it. In general, older children reacted more severely than younger ones, the sexes being equally affected. Reactions to second and third intramuscular injections were slightly more severe after a primary subcutaneous than after a primary intramuscular injection. *M. Lubran*

INDUSTRIAL MEDICINE

226. **The Industrial Hygiene of Uranium Fabrication**
W. B. HARRIS and I. KINGSLEY. *A.M.A. Archives of Industrial Health* [*A.M.A. Arch. industr. Hlth*] **19**, 540–565, May, 1959. 8 figs., 7 refs.

Uranium in one form or another is the basic material used to fuel nuclear reactors. In the manufacture of fuel elements uranium may be harmful because of its chemical and radioactive properties. For practical purposes the main health hazard is from inhalation of particles of uranium or its compounds. Since uranium is readily oxidized air-borne dispersion can result from all processing in which heat is generated. This property also creates a fire risk, with the consequent release of toxic fumes in addition to damage from fire. The only health hazard with solid material comes from prolonged handling.

In this paper from the U.S. Atomic Energy Commission, New York, measures to reduce health hazards in a number of metallurgical and fabricating techniques are described. The loss of material inherent in the use of gas-fired furnaces for heating uranium, as well as the health risk, have led to the introduction of a salt bath furnace and the use of a mixture of lithium and potassium salts. A coating is thus formed which effectively prevents oxidation and reduces air contamination. In addition exhaust ventilation with an air flow of 500 c. ft. per minute per sq. ft. (152 c. m. per minute per sq. m.) of hood area and a minimum velocity of 50 ft. (15·24 m.) per minute has been successful. The use of grated floors to prevent contamination of the atmosphere from foot scuffling of the oxide scale is recommended and cooling by immersion quenching or by air is generally satisfactory. Although reasonably low exposures can be expected from these measures in manual operations, even better results can be obtained by automatic operation using a salt bath. Exposure during hammer forging and hammering can be controlled by the same measures, although this may be difficult; in particular the floor needs attention, for many forging shops are covered with a layer of cinders. In machining uranium the danger of fire is the first consideration. The site of operation should be flooded with coolant and low cutting speeds employed. To prevent air contamination the fitting of hoods over lathes and other tools must be insisted upon and local exhaust ventilation to be effective requires reasonably complete enclosure of the machine. In the disposal of waste attention should be paid to accepted permitted levels of contamination by uranium.

The application of general health and safety controls to all the processes is discussed. Good " housekeeping " is essential and to secure this the use of brooms should be prohibited, reliance being placed on vacuum cleaning. Measures for personal protection include the wearing of leather gloves for prolonged handling of metal and of ordinary protective clothing. Eating at work should not be permitted.

[This is an interesting study of the control of these processes from the standpoind of occupational hygiene. The authors do not attempt to consider the medical supervision of employees.] *R. E. Lane*

227. **Allergy to Gum Arabic in Printers.** (L'allergie à la gomme arabique des imprimeurs)
J. TURIAF, J. TABART, M. SENÈZE, and D. VERNIER. *Semaine des hôpitaux de Paris* [*Sem. Hôp. Paris*] **35**, 1907–1914, June 4, 1959. 19 refs.

Allergic reaction to the use of gum arabic was first reported in 1933, and similar reactions to exposure to gum tragacanth and gum acacia have been reported. In the printing trade letterpress printers in black and in colour and offset craftsmen are heavily exposed to gum arabic, and binders to a lesser degree, an alcoholic solution of gum arabic being sprayed upon each printed sheet as it emerges from the press to prevent adhesion and to form a protective screen against staining. The air in some shops may contain gum arabic to the extent of 45 or 50 mg. per c.m., and at the close of the day's work it may be impossible to see clearly from one end of the shop to the other, so dense is the mist.

The investigation here reported from the Hôpital Bichat, Paris, followed upon the discovery of the effects of his work upon a typographer who, within a few months of starting work in the black letterpress printing shop, developed an irritation of the eyes and nose, progressing to attacks of acute coryza and rhinitis and, finally, after 10 years' employment, to bronchial asthma. This asthma became more and more severe until after any 2

consecutive days at work he needed 3 days' sick leave for recovery. On removal from contact with gum arabic he recovered completely. (This case is described in detail.) An inquiry was then undertaken in a large printing works in Paris. Of 150 workers questioned 105 replied, of whom 74 were employed in letterpress printing. Of these 74, 51 had been subject to allergic complaints such as spasmodic coryza, asthma, conjunctivitis, pruritus, and neuralgic headache; 23 were fully examined and the findings are given in tabular form. Rhinitis was by far the most common complaint, beginning within a few months of the start of exposure and frequently leading to asthma after a latent period of one to 20 years. Classic bronchial asthma was present in 12 of the 23 men studied. There was an accompanying eosinophilia, and eosinophil granulocytes were found in the abundant sputum. At first dyspnoea was noticed only some hours after the start of the day's work, and cleared up completely on emerging into clean air at the close of the shift, but it steadily increased in severity until it became incapacitating, necessitating the transfer of the employee to work out of contact with the gum. Ocular symptoms such as injection of the conjunctivae and swelling of the eyelids came on during the first hours of the day's work, persisting through the shift and resolving again fairly quickly on escape from the contaminated atmosphere. Skin complaints included pruritus, generally mild and involving the hands, the flexor aspect of the forearms, and the neck, but occasionally generalized, and a dry, desquamating, superficial eczema which was always discrete, affecting the eyelids, the groove behind the ears, and folds in the skin of the face and hands. The various allergic manifestations were combined; an isolated symptom was rare. All were cured by removal from an atmosphere contaminated with gum arabic. Intravenous injection of gum arabic, if repeated, is capable of inducing the same effects—lacrimation, nasal catarrh, cough, and bronchial wheezing—all of which are rapidly controlled by the administration of ephedrine.

As yet there is no statutory control, but it is recommended that allergy in workers with gum arabic should be recognized in future as an occupational disease.

M. A. Dobbin Crawford

228. **Controlled Human Exposures to Malathion Aerosols**
H. H. Golz. *A.M.A. Archives of Industrial Health* [*A.M.A. Arch. industr. Hlth*] **19**, 516–523, May, 1959. 4 figs., 6 refs.

The hazards of exposure to many of the commonly used organic phosphate insecticides are now well known and have restricted their wider use. In 1954, however, the compound malathion, the diethylsuccinate of dimethyldithiophosphoric acid, was introduced and has proved to have none of the dangerous properties of, for example, parathion. In this study, undertaken to investigate the susceptibility of man to malathion, 3 sets of aerosol "bombs" were used; one of these (for the control group) contained only the basic propellant vehicle, while the other two contained respectively 5% and 20% of premier grade (95%) malathion. The subjects were 16 healthy male volunteer prisoners, and all the exposures were made in solitary-confinement cells each of which had a capacity of approximately 1,700 cubic feet (48 c. metres), the only opening into the cell being covered with plywood during the experiment so as to minimize air movement. The concentrations achieved were much higher than might reasonably be expected to occur during the domestic use of malathion aerosols likely to become commercially available to the public.

Careful observations of the effects of 84 exposures on 43 consecutive days failed to demonstrate any significant effect of malathion. The erythrocyte cholinesterase activity never fell below 90% of normal except on 2 occasions, and these two aberrant results are attributed to technical error. An observed decreased plasma cholinesterase activity also was not thought to be due to malathion absorption. The author concludes that aerosol bombs containing 5% of malathion are safe for domestic use so far as the malathion content is concerned.

R. G. Meyer

229. **The Biological Effects of Vanadium. II. The Signs and Symptoms of Occupational Vanadium Exposure**
C. E. Lewis. *A.M.A. Archives of Industrial Health* [*A.M.A. Arch. industr. Hlth*] **19**, 497–503, 1959. 7 refs.

The biological effects of vanadium have been investigated by the author in 24 men ranging in age from 38 to 60 years who had been exposed to vanadium at their work for at least 6 months; 45 men of the same age range not so exposed served as controls. The investigation included a careful history, physical examination, electrocardiography, analysis of the urine, and determinations of the haematocrit value, serum cholesterol level, and urinary excretion of vanadium. In addition an analysis was made of samples of air and dust in the plants at which the men were employed.

The examination showed that irritation of the eyes, nose, throat, and respiratory tract was present in 15 (62%) of the exposed group and green coloration of the tongue in 9 (37%). The examinations revealed no evidence of chronic intoxication or injury attributable to exposure to vanadium.

A comparison of these findings with those of studies reported from Sweden, Peru, Germany, and England showed that they agreed in the main. The clinical picture common to all groups studied is that of irritation of the mucous membranes, which can result in a chronic productive cough and, except in the Swedish study in which it was inexplicably absent, greenish discoloration of the tongue. Although there is so far no evidence to indicate that the chronic bronchitis observed in vanadium workers might have more serious and permanent sequelae, the author considers that because of the known effects of vanadium dust persons with arrested tuberculosis or chronic lung disease should be excluded from exposure to this hazard. The examination of air samples showed that the air content of vanadium ranged, with one exception, between 0·1 and 0·3 mg. per c. metre. It was noted that the serum cholesterol levels in the workers exposed to vanadium were significantly lower than those in the controls.

R. G. Meyer

Anaesthetics

230. **Preliminary Clinical Study of Dipipanone Hydrochloride (Pipadone) in Anaesthesia**
L. LAMOUREUX, F. SHOONER, and L. TREMBLAY. *Canadian Medical Association Journal* [*Canad. med. Ass. J.*] **80**, 968–973, June 15, 1959. 1 fig., 14 refs.

From the Notre-Dame Hospital, Montreal, the authors describe their experience with dipipanone hydrochloride (" pipadone ") as an analgesic and as a premedicament in anaesthesia. When 25 mg. of the drug was injected intravenously over one minute for premedication respiratory depression was marked, there being slowing of respiration with increased tidal volume, the total effect being a slight reduction in minute volume. After the intravenous injection of 10 mg. of pipadone over 2 minutes in 25 patients under thiopentone anaesthesia apnoea lasting 15 minutes occurred, followed by great depression of respiration. In some cases bradycardia after a brief period of tachycardia was observed, and in 4 out of 25 cases a fall in blood pressure ranging from 25 to 40 mm. Hg occurred in the horizontal position and in a further 5 on tilting the table foot-down. To 155 patients dipipanone was given intramuscularly as a postoperative analgesic, its effect being assessed by the patient's indifference to pain. Analgesia appeared to last about 4 hours, and though incomplete with the first dose of 20 mg., was often completely effective after a second dose, suggesting a slight accumulative effect. In a comparative test 100 mg. of meperidine was shown to be less effective than 25 mg. of dipipanone [but in the abstracter's opinion the number of patients subjected to the test (14) was too small to allow of any significant conclusion].

Sleep was not produced during dipipanone analgesia, and electroencephalograms did not show the characteristic sleep pattern; this may be an advantage in some neurosurgical operations. After analgesia with nitrous oxide and dipipanone 3 patients given large doses (25 to 35 mg.) were difficult to rouse, but in most cases the patient was tranquil and cooperative and responded to verbal commands, but was without amnesia. Complete depression of the cough reflex, useful in many operations, was observed in 90 patients. The authors also recommend dipipanone for pneumography and arteriography, given by intravenous drip infusion in 0·05% solution to a total dose of between 10 and 35 mg.; the vomiting which commonly follows these procedures occurred in only 3% of 148 patients. In 47 out of 60 patients undergoing rhinoplasty dipipanone was given by intravenous drip infusion to maintain the blood pressure at 70 to 80 mm. Hg so as to reduce bleeding. The authors recommend its use also for ophthalmological operations, in which the eye remains still, while there is corneal analgesia and myosis; of 21 ophthalmological patients, only 2 vomited postoperatively. The secondary effects of the drug were rarely troublesome or severe; of a large number of patients, only 2 to 3% suffered from postoperative vomiting and 2% from urinary retention.

Raymond Vale

231. **Two Thousand Cases of Fluothane Anaesthesia**
D. J. L. MACWATT, P. E. O'SHAUGHNESSY, and D. J. POWER. *Canadian Medical Association Journal* [*Canad. med. Ass. J.*] **80**, 973–976, June 15, 1959. 3 figs., 5 refs.

In this paper from St. Mary's Hospital, Montreal, the authors report their results with " fluothane " (halothane) in 2,000 cases in which this agent was used as an adjunct to light anaesthesia in patients aged between 3 weeks and 87 years, many with complicating hepatic or renal disease, diabetes, cardiac failure, or thyrotoxicosis. Over half were undergoing major surgical procedures. They stress the need for adequate preoperative atropinization, without which bradycardia, hypotension, and extrasystoles were frequent. Induction was by the " open-drop " method in infants, with nitrous-oxide–oxygen and halothane in older children, and in adults with thiopentone. Relaxation for intubation was achieved with graded doses of succinylcholine chloride, except in the case of infants. Maintenance of anaesthesia was by " open-drop " halothane with oxygen in infants and by semi-open nitrous-oxide–oxygen and halothane in children and adults, an apparatus with a non-return valve for the former and a circle absorption system for the latter being employed.

The authors consider that a vaporizer which delivers a greater concentration than 2 to 3% should be avoided, and calibration of the percentages delivered is desirable. They found that respiratory depression was unusual in this series. Relaxant drugs were used to produce relaxation since early attempts to produce it with halothane alone were either inadequate or produced hypotension and hypopnoea. They noted that the dose of succinylcholine chloride required was smaller with halothane than when meperidine was used. Tubocurarine was satisfactory and no more likely to produce bradycardia and hypotension than other relaxants. Pulse rates slowed in proportion to the depth of anaesthesia, such slowing being more marked in the aged or in patients not given atropine. Pulse rates were higher when gallamine was used as the relaxant owing to the effect of this drug on the vagus. Hypotension of small degree occurred in many patients, but was without consequence; in 5 cases halothane was used as a hypotensive agent in higher concentrations, but this produced respiratory depression, bradycardia, and extrasystoles. In 8 cases phenacylhomatropinium chloride (" trophenium ") was given along with halothane with excellent results. After anaesthesia the return of consciousness was rapid and vomiting was infrequent. *Raymond Vale*

Radiology

232. **Fetal Exposure to Diagnostic X Rays, and Leukemia and Other Malignant Diseases in Childhood**
D. D. FORD, J. C. S. PATERSON, and W. L. TREUTING. *Journal of the National Cancer Institute* [*J. nat. Cancer Inst.*] **22**, 1093–1104, June, 1959. 7 refs.

In a study of the relationship between antenatal exposure to x rays and the occurrence of malignant disease in childhood carried out at Tulane University, New Orleans, the case histories of all children under 10 years of age who were certified to have died in the State of Louisiana from leukaemia or other malignant disease during the period 1951–5 were reviewed. Data relating to the relevant pregnancy were extracted from the corresponding birth certificates, and inquiries were addressed to the doctors in attendance at the delivery concerning possible exposure of the foetus to irradiation *in utero*. Similar information was also obtained for a group of control children who had died in Louisiana from other causes during the same period. Adequate information was obtained for 458 of the 852 children initially studied —78 out of 117 who had died of leukaemia, 74 out of 127 who had died of other malignant disease, and 306 out of 608 who had died of other causes. Analysis of the cases which were eliminated showed no reason to suppose that the lack of information for all the patients in each group would introduce any bias into the results.

The frequency of exposure to diagnostic x rays *in utero* was greater for the children who had died of leukaemia (26·9%) and for the children who had died of other malignant disease (28·4%) than for the control children (18·3%). In all but 2 cases the exposure was the result of radiography of the mother's abdomen or pelvis for obstetric reasons during the last trimester of pregnancy. The 2 exceptions were in control children whose mothers underwent intravenous pyelography during the second month of their pregnancy. The differences in frequency of irradiation were not statistically significant, but the extent of the difference was closely similar to that observed in the large series reported by Stewart *et al.* (*Brit. med. J.*, 1958, **1**, 1495; *Abstr. Wld Med.*, 1958, **24**, 458). The relative risk of death from malignant disease in the exposed group compared with that in the non-exposed group was 2·1:1 in Stewart's study and 1·7:1 in the present study. The difference was observed both in children dying at ages 0 to 4 years and in those dying at ages 5 to 9 years and was observed for each of the main types of malignant disease. The difference was, moreover, greater for repeated exposure than for a single exposure. Stewart's data were obtained directly from the parents, and the control subjects were living children. The present data were obtained uniformly from professional sources, and the controls were children who had died of non-malignant causes. It is striking that despite these differences in technique the results were so alike.

[A confusing element in the analysis of the figures is that the frequency of irradiation was lower for coloured children than for white children and the proportions of coloured children in the 3 groups were different. These differences cannot, however, account for the positive results.] *Richard Doll*

EXPERIMENTAL

233. **An Experimental Study of the Effect of Irradiation on the Dissemination of Cancer**
P. D. OLCH, R. V. ECK, and R. R. SMITH. *Cancer Research* [*Cancer Res.*] **19**, 464–467, June, 1959. 3 figs., 7 refs.

The work here described from the National Cancer Institute, U.S. Public Health Service, and which forms part of a planned research scheme was designed to study the viability of metastasizing cells from irradiated tumours by a method which excludes confusion with metastases possibly existing before the irradiation.

Cloudman S91 melanoma tumours growing intramuscularly in rats were irradiated (275 kV., 3,000 r. in 8 minutes), and suspensions of living tumour cells were then injected intravenously into healthy untreated rats to produce "artificial pulmonary metastases"; the inoculations were carried out at intervals varying from 3 hours to 20 days after the irradiation. Three weeks after the inoculation the recipient rats were killed and examination of the lung tumours present showed that there was a marked reduction in both the number and size of these "metastases" as compared with control animals which had received non-irradiated tumour cells. The effect was already marked 3 hours after irradiation, reached its maximum after 3 days, and was almost *nil* at 20 days after irradiation. Also no irradiated tumour produced as many or as large metastases as the untreated control tumours, thus demonstrating a reduction in both the viability and the growth potential of the cells in all cases.

Further work on these lines is being carried out.
E. Stanley Lee

234. **Effects of Total-body Irradiation on the Production of Antibody in Man**
I. L. STOLOFF, F. I. HAURANI, E. F. REPPLINGER, and W. P. HAVENS. *New England Journal of Medicine* [*New Engl. J. Med.*] **260**, 1258–1261, June 18, 1959. 2 figs., 7 refs.

At the Jefferson Medical College of Philadelphia the authors have studied the effects of whole-body irradiation on the production of antibodies in 6 patients with acute leukaemia and one with disseminated neuroblastoma, the patients' ages ranging from 5 to 41 years. Whole-body irradiation was delivered to 6 of the patients

by a 250-kV. x-ray machine, while the seventh was irradiated with a cobalt teletherapy apparatus. The mid-plane dose varied from 170 to 800 r. After irradiation the patients received homologous bone marrow from 9 healthy donors. The authors then investigated the ability of the patient to produce antibodies to one antigen (diphtheria toxin) and also the question whether the infused homologous marrow cells could produce antibody to another antigen (tetanus toxoid). The patients were all shown to be Schick-negative before receiving the diphtheria toxoid.

In the 5 patients who received 490 r. or less the response to the toxoid was similar to that of a normal person, there being a significant increase in the antitoxin titre by the 7th day, reaching a maximum between 14 and 28 days after inoculation. There was no relationship between the immunological response and the degree of lymphopenia or neutropenia that occurred. The 2 patients who received 800 r. showed no increase in circulating antitoxin. Of the 9 donors of bone marrow, 7 had previously been immunized against tetanus, having been inoculated with tetanus toxoid 2 to 15 days before donating their bone marrow to 6 of the 7 irradiated patients. These 6 patients failed to show any significant alteration in the amount of circulating tetanus antitoxin.

M. P. Cole

RADIODIAGNOSIS

235. **Great Vessel Involvement in Lung Cancer: Angiocardiographic Report on 250 Consecutive Proved Cases**
I. STEINBERG and N. FINBY. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **81**, 807–818, May, 1959. 11 figs., 17 refs.

At the New York Hospital–Cornell Medical Center, New York, the authors have carried out angiocardiography on 150 further cases of cancer of the lung and, adding these to 100 cases previously reported (Steinberg and Dotter, *Arch. Surg.* (*Chicago*), 1952, **64**, 10; *Abstr. Wld Med.*, 1952, **12**, 22), now present their conclusions based on the total of 250 cases. All examinations were made during inspiration with the patient in the erect sitting position without an anaesthetic, one injection of 50 ml. of 70% sodium acetrizoate being given for the frontal view and a second similar injection for the lateral or oblique projection. No fatalities or troublesome reactions occurred despite the double injection.

The most striking abnormalities occurred in cases with hilar or mediastinal involvement extending to the superior vena cava or in cases of stenosis of one of the pulmonary arteries, changes of this type being present in some 30% of the series. The remaining 70% consisted of cases of peripherally situated tumours, and in many of them lobar or segmental arterial involvement was demonstrated. The authors stress that these changes are in no way specific for lung cancer and may occur in non-malignant conditions also. The chief value of the method is in assessing operability, although it must be realized that such an estimate based on angiocardiographic findings may be unduly optimistic in some cases. Angiocardiography is also useful in cases of bilateral pulmonary disease, in which a precise evaluation of the pulmonary circulation may be of great value in preventing pneumonectomy being performed on patients who have not the respiratory reserve to stand such an operation.

D. E. Fletcher

236. **New Technique of Contrast Visualization of the Distal Aorta, Pelvic and Lower Extremity Arterial System in Obliterative Vascular Disease**
B. P. SAMMONS and H. P. MAHIN. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **81**, 835–840, May, 1959. 7 figs., 9 refs.

Occlusive arterial disease of the aorta or iliac arteries can be demonstrated in various ways—for example, by means of translumbar aortography, with the slight chance of a serious complication, or by the Seldinger technique of retrograde femoral catheterization of the aorta, but both these methods have a number of disadvantages. The authors describe a technique practised at the U.S. Naval Hospital, St. Albans, Long Island, which is easy to perform and probably safer than either of the two methods mentioned.

Essentially the technique consists in percutaneous retrograde injection of the femoral artery on the less involved side and the rapid injection of 35 ml. of 50% "hypaque" by hand, a tourniquet being placed around the thigh as high as possible below the injection site; during the injection the patient performs the Valsalva manœuvre to slow the flow of blood. Good films are obtained of both iliac and pelvic arteries and the lower aorta, while the use of a portable set in addition enables films to be taken of the femoral and popliteal arteries on the opposite side. After the first injection the tourniquet is removed and a further small injection made so as to demonstrate the femoral and popliteal arteries on the side of the puncture. If this examination reveals the lower edge of an aortic block the upper end of the block can then be demonstrated by performing percutaneous lumbar aortography with 10 ml. of 50% hypaque. This procedure has been carried out in 86 cases so far without significant morbidity.

D. E. Fletcher

237. **Barium Sulfate and Bismuth Subcarbonate Suspensions as Bronchographic Contrast Media**
S. W. NELSON, A. CHRISTOFORIDIS, and P. C. PRATT. *Radiology* [*Radiology*] **72**, 829–838, June, 1959. 10 figs., 12 refs.

Although iodine-containing contrast media are relatively safe to use in bronchography, they are by no means ideal. Working at the Ohio State University Health Center, Columbus, the authors tried barium sulphate or bismuth subcarbonate for this purpose. They began by injecting various contrast agents into the trachea of rabbits, which were subsequently killed and the lungs examined. The four agents used were oily "dionosil" (propyliodone), barium sulphate, "lipiodol" (iodized oil), and bismuth subcarbonate. It was found that all the media produced a foreign-body reaction in the lung,

which was most severe with bismuth subcarbonate; 10 weeks after the experiment none of the other 3 media was retained in the lungs, nor was there any histological change at that time.

Bronchography was then carried out in 100 patients, 50 receiving oily dionosil and 50 receiving a barium sulphate suspension in the form of 20 g. of "micropaque" in 40 ml. of normal saline containing 1·5% carboxymethylcellulose. Excellent bronchograms were obtained with little alveolar filling in the 50 cases in which barium sulphate was used. The patient's reaction was recorded by noting the pulse and temperature for 24 hours, the reaction to barium being less than that to dionosil. The authors consider that increasing the carboxymethylcellulose to 2 or 3% would further improve results. *D. E. Fletcher*

238. **Biphasic Radiography of the Thorax: a Method of Investigation of the Function of the Lungs.** (Двухфазная рентгенограмма — метод исследования функции легких)

A. I. JAKOVLEV. *Вестник Рентгенологии и Радиологии* [*Vestn. Rentgenol. Radiol.*] **34**, 14–18, May–June, 1959. 4 figs., 16 refs.

The method described by the author consists in taking two radiographs of the chest, one in deep inspiration and the other in forced expiration, through a grating consisting of vertical strips of lead separated by clear strips of the same width. Comparison of the density of the light and dark stripes on the radiograph gives an indication of the condition of the lung in each of the two phases, the densities being measured by means of a photometer. Biphasic radiography also enables the mobility of all the anatomical units taking part in the act of respiration to be measured and an estimate of respiratory function to be made. Thus displacement of the diaphragm by 1 cm. is stated to correspond to an inspired volume of 200 ml. and a similar displacement of the posterior segment of the 5th rib to an inspired volume of 500 ml. Details of construction of the lead grating and of an aluminium step-photometer are given. *A. Orley*

239. **A Comparison of Techniques for Visualization of the Coronary Arteries**

J. I. FABRIKANT, W. G. ANLYAN, G. J. BAYLIN, and R. B. TRUMBO. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **81**, 764–771, May, 1959. 9 figs., 14 refs.

In the study here reported from Duke University School of Medicine, Durham, N. Carolina, which was designed to evaluate various techniques in an attempt to find the safest and most reliable method of coronary arteriography, myocardial infarction was produced experimentally in 46 dogs by ligation of the left anterior descending coronary artery, arteriograms being obtained one week before ligation and again 2 to 6 weeks after it, when the animals were killed and examined within 48 hours.

The following technique was found to be the most satisfactory. The anaesthetized dog was maintained on a slow intravenous drip infusion of normal saline through a polyethylene catheter inserted into the jugular vein. The common carotid artery on the same side was then occluded with a silk suture after a No. 8 woven intra-arterial catheter had been inserted retrogradely to a distance of about 15 cm. where, under fluoroscopic control, the tip of the catheter was placed at the junction of the ascending aorta and the brachiocephalic artery; this manœuvre was facilitated by introducing small bursts of 50% "hypaque". The catheter was then connected to a syringe containing 25 to 50 ml. of 50% hypaque, and an automatic injector capable of producing a pressure of 120 lb. per sq. inch [8·44 kg. per sq. cm.], which experiment had shown to be superior to hand injections, was charged in readiness. Cardiac arrest was then produced with 4 to 8 mg. of acetylcholine injected intravenously and 3 seconds after asystole, as shown on the electrocardiogram, the firing mechanism of the automatic injector was released and the opaque medium injected over 4 seconds, the exposure being made when only 5 ml. of medium remained to be injected. Cardiac arrest with acetylcholine did not produce any residual damage and no death could be attributed to it. A single exposure using a Potter Bucky grid was found to be superior to the Schonander multiple exposure technique. *John H. L. Conway-Hughes*

240. **Coronary Arteriography**

J. S. LEHMAN, R. A. BOYER, and F. S. WINTER. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **81**, 749–763, May, 1959. 13 figs., 14 refs.

From Hahnemann Medical College and Hospital, Philadelphia, the authors present an analysis of the results of catheter thoracic aortography (44 cases), cardiac ventriculography with transthoracic needle puncture of the ventricle (230 cases), and suprasternal transaortic coronary arteriography (107 cases), all three methods having been employed in attempts to opacify the coronary arteries. More recently they have combined cardiac arrest, induced with acetylcholine, with catheter thoracic aortography and suprasternal aortic needle puncture. Patients under 14 years of age were excluded from the analysis, although in fact the catheter thoracic aortic studies gave the best results in children. All the examinations were confined to serial filming in a single plane. In the earlier studies the usual opaque medium was 70% diodone, but more recently they have used 85 or 90% "hypaque", the amounts varying from 20 to 45 ml., this being injected rapidly by means of a mechanical pressure injector in a period of 2 seconds.

They conclude from these studies that cardiac ventriculography produces coronary arterial opacification with considerable frequency (202 cases out of 230), but dense opacification of the left ventricular cavity may obscure portions of the coronary arteries. The procedure is not, however, without its hazards and the authors do not regard it as the method of choice. Suprasternal needle puncture is also not without danger, and the possibilities of intramural aortic injection of opaque medium and bleeding have to be borne in mind. In

general it is considered that further experience is necessary before the usefulness of these procedures can be established. Catheter thoracic aortography appears to be the most efficacious method of obtaining good visualization of the coronary arterial tree. The risks of this method are principally those related to malposition of the catheter tip, together with those incident to the subsequent repair or closure of the artery through which the catheter is inserted. Coronary arteriography during cardiac arrest seems to merit further investigation, but the potential hazards of this procedure are as yet unknown. Momentary occlusion of the aorta or the introduction of double-lumen catheters with a distensible balloon have resulted in good opacification in experimental animals, but the application of these methods to man may carry too great a risk. Cinefluorography would appear to offer certain added advantages. However, the variability of the coronary arterial system makes interpretation difficult whatever the method used. The arteriographic diagnosis of coronary arterial disease rests on the demonstration of irregularity of the lumen, manifested by abnormal narrowing or tapering. It is recalled that absence of, or incomplete, filling of the arteries may be due to an insufficiency of contrast medium to effect complete filling.

John H. L. Conway-Hughes

241. **Functional Ascending Phlebography of the Lower Extremity by Serial Long Film Technique: Evaluation of Anatomic and Functional Detail in 62 Extremities**
J. A. DeWeese and S. M. Rogoff. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **81**, 841–854, May, 1959. 8 figs., 19 refs.

The authors describe from the Strong Memorial Hospital, Rochester, New York, their technique of "functional ascending phlebography" for the demonstration of the deep veins of the leg and discuss the results of such examination of 62 extremities. The procedure is carried out on the x-ray table, which is raised head-up 60 degrees from the horizontal, and 40 ml. of 50% "hypaque" is injected into a foot vein, a rubber tourniquet being applied to occlude the superficial veins above the ankle. A radiograph is then taken of the whole limb on two films each measuring 17×14 inches (43×35·5 cm.) placed end to end in a 36×14-inch (91·5×35·5-cm.) cassette located beneath a specially long Bucky grid permanently mounted under the table top. An anode–film distance of 56 inches (142 cm.) is necessary to cover a film of this size.

After the first film has been exposed the tourniquet is removed and the patient asked to raise himself forcibly on his toes 10 times, after which a second exposure is made. Finally in most cases a third film (17×14) inches centred under the pelvic region is exposed 45 seconds after the second film. The technique produces good filling of the anterior tibial, posterior tibial, peroneal, and superficial femoral veins in most cases, but the deep femoral vein is less often visualized. After outlining the findings in normal extremities the authors describe the appearances in patients with varicose veins and after phlebitis. In the latter group the deep veins were often irregular, tortuous, and valveless, but notably were not dilated; there was, however, a definite increase in the number of communicating and collateral veins. In patients with varicose veins the majority of the deep vessels were normal, but some showed smooth dilatation and were without valves. Finally a study of venous function showed that the rate of emptying of the veins was correlated with the presence or absence of valves and with the number of collateral and communicating veins. In the presence of normal veins in the thigh and of only a few communicating branches the majority of deep veins in the calf of the leg showed good to excellent emptying.

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242. **The Bone Lesions of Childhood Leukemia: a Survey of 140 Cases**
J. K. V. Willson. *Radiology* [*Radiology*] **72**, 672–681, May, 1959. 8 figs., 18 refs.

The diagnostic value in leukaemia in childhood of lesions of the long bones was studied in 140 cases seen at Johns Hopkins Hospital, Baltimore. Radiologically, bone changes were present in 89 (64%) of the patients, 74 of whom, predominantly males and white children, were between 2 and 10 years of age. Extensive destructive lesions were observed, which on the whole presented a characteristic pattern, with areas of rapid bone growth being peculiarly liable to involvement. Metaphysial bands of translucency were the most common finding (76 cases) and were usually seen at the knees and wrists. Of 740 consecutive radiographs of the long bones obtained over a period of one year 32 revealed this transverse translucent line of the metaphyses; none of the 32 patients had leukaemia and only 4 were over 2 years of age. The author therefore considers that this finding is non-specific below that age. In leukaemia, unlike scurvy, the lateral cortical margins and the metaphysial plates are usually intact. In 53 cases osteolytic lesions were found in the spongiosa of the long bones, varying from punctate areas of increased translucency to zones of frank destruction. In some cases extensive areas of metaphysial decalcification may suggest that the metaphysial band has expanded to include the spongiosa. In 3 cases infractions of such areas were noted. Pathologically, these destructive lesions are attributed to interference with nutrition and pressure by the proliferating leukaemic tissue, with increased osteolysis. Periosteal elevation along the shafts of the long bones, due to leukaemic infiltration between the cortex and the periosteum, was evident in 27 cases. Radiographs of the long bones in cases resembling leukaemia clinically, including 25 of rheumatoid arthritis and 20 of anaemia, did not show the transverse translucent line at the metaphysis, the osteolytic lesions, or the periosteal elevation seen in leukaemia. In metastatic neuroblastoma the radiological picture may be comparable, but without the transverse metaphysial band of translucency and with a greater tendency to central, rather than peripheral, bone involvement. The author concludes that radiographs of the long bones may be of value when leukaemia is suspected, especially in patients over the age of 2 years.

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